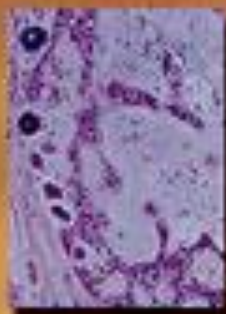


CONTEMPORARY ORAL AND MAXILLOFACIAL PATHOLOGY

SECOND EDITION



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Lewis R. Eversole
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CONTEMPORARY ORAL AND MAXILLOFACIAL PATHOLOGY, second edition

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Dedication

To present and future students and clinicians who possess an ardent desire to be truly knowledgeable of the oral and maxillofacial diseases that afflict humankind.



Preface

The second edition of *Contemporary Oral and Maxillofacial Pathology* is newly formatted and presents a substantial expansion in the number of diseases. During the intervening years since the publication of the first edition, the knowledge base and concepts of many entities have undergone significant changes, particularly in the realm of the infectious, immunologic, and blood diseases. Many new medications have evolved and have been integrated into the treatment sections of the applicable diseases.

The second edition continues to retain the primary focus of being a concise, user-friendly resource for those wishing to acquire a solid working knowledge of the oral diseases affecting the oral and maxillofacial regions. Providing essential information in a compact and lightweight book rather than in a reference resource for all diseases occurring in the anatomic area continues to be its highest priority. Thus deciding which disease entities *not* to include continued to be a challenge. Decisions to exclude specific diseases were basically made on their incidence of occurrence in the Western world.

The chapter sequence remains unchanged, progressing from subject material requiring less prerequisite basic science knowledge to those requiring more encompassing information. The new two-column format allows for a sizeable increase in the size and number of illustrations, substantially enhancing the atlas and diagrammatic component of the text. Most of the diagrammatic illustrations have been redrawn with an added dimension of professionalism. The sections devoted to the embryonic, molecular, and genetic sciences basic to groups of disease processes have been extended and updated. The inclusion of this content is based on the belief that understanding the biologic basis of disease increases the clinician's diagnostic acumen when patients present features of diseases that differ from the classic norm. Free, universal Internet access to worldwide medical literature has reduced the usefulness of extensive citations in the *Additional Readings* sections after each chapter. Thus the number of citations has been substantially reduced and appropriately updated with recent and pertinent titles.

Chapter 1, *Developmental Disturbances of the Oral Region*, is expanded to include more of the commonly encountered craniofacial syndromes and their gene loci. Chapter 4, *Bone Lesions*, is updated, and the most recent

advances in the basic knowledge of bone cell differentiation and metabolism have been added. Chapter 6, *Epithelial Disorders*, is expanded to include additional skin lesions commonly found on the face. The section on carcinogenesis has been revised to reflect the latest concepts regarding the effect of oncogenic factors on the cell-cycle signaling system and the development of oral carcinoma. Chapter 7, *Oral Infections*, is substantially updated, particularly the information pertinent to the mechanism of acquiring HIV infection, the development of AIDS, and oral implications. Additionally, Chapter 7 includes recent knowledge regarding the expansion of the herpes family of viruses and the new drugs used in their management. Chapter 8, *Immune-Mediated Disorders*, has been updated to contain significant advances in the understanding of the desquamative mucosal diseases, which in some cases have resulted in some new nomenclature, the basis for diagnosis, and disease management. Within Chapter 8, the category of diseases with a possible immune basis has been expanded to include the diseases now grouped under the broad heading of orofacial granulomatosis and the chronic inflammatory gastrointestinal diseases with oral manifestations. Chapter 9, *Connective Tissue Lesions*, has been broadened and updated to include the recently defined subcategory of lesions whose primary cellular component is the myofibroblast. Chapter 10, *Salivary Gland Disorders*, has been embellished to include some of the less encountered salivary gland adenomas and adenocarcinomas. These disorders have been added primarily as a convenient resource for the maxillofacial and head and neck surgical specialists. Except for the addition of a few additional tongue lesions, Chapter 11, *Physical and Chemical Injuries*, has remained relatively unchanged. The information regarding the non-Hodgkin lymphomas in Chapter 12, *Diseases of Blood*, has been revised to reflect significant new changes in concept, classification, and understanding of these diseases. Information relative to a specific variant of non-Hodgkin lymphoma that arises within the oral mucosa, adjacent structures, and throughout the digestive tract known as *MALToma* has been expanded to reflect recent advances.

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Acknowledgments to the First Edition

The production of a textbook in a specialized field is the culmination of many years of contemplating fundamental principles conveyed by early mentors; continually scrutinizing the literature to remain abreast of advances; and ardently collecting, developing, and refining illustrative material. Many of these activities can only be achieved with the help of professional colleagues. To those colleagues with whom the authors have interacted and benefited professionally, a heart-felt thanks is extended.

Particular acknowledgment is extended to Dr. William G. Shafer and the late Dr. Donald A. Kerr for their guidance and direction during the introductory and formative years of our careers. A special thanks is extended to Dr. David G. Gardner who provided collegial advice during the early academic years of one of the authors (JPS) and who willingly shared in the compilation of visual teaching materials, some of which appear in this textbook without specific acknowledgment.

Contemporary Oral and Maxillofacial Pathology would not have been possible without the help and cooperation of past and present colleagues with whom the authors have closely worked. Many of the illustrations are teaching materials collectively procured and shared with these colleagues. Special thanks and appreciation are extended to Dr. Tom Daley, University of Western Ontario; Dr. Russell Christensen and Dr. Frank Lucatorto, University of California, Los Angeles; Dr. Alan Leider, University of the Pacific; Dr. Ron Baughman, University of Florida; and Dr. William Sabes. For any images

that were inadvertently not acknowledged, we apologize. Every effort was made to follow up on any available information that would identify the actual source of the material that was in the teaching collections of the authors and used in this text. Since the origin of some of the material extends beyond a 20-year period, this was occasionally difficult.

We wish to acknowledge the exquisite computer-generated graphic illustrations produced by Mr. Patrick Masson of the UCLA School of Dentistry Illustration and Media Center and the help he provided during the preparation of the book.

We would also like to thank the editorial and production staff of Mosby, especially Ms. Linda Duncan, the editor of the project, for her guidance, vision, and support in bringing the concept of the book to reality; Ms. Jo Salway, developmental editor; and Ms. Cheryl Abbott Bozzay, a very competent and highly professional production editor, for keeping the project under control at all times and for her patience, help, and understanding throughout the most difficult periods.

Finally, a special thanks is extended to our families, friends, and colleagues who were neglected in various ways during the arduous hours required to see the project to fruition.

**J. Philip Sapp
Lewis R. Eversole
George P. Wysocki**



Acknowledgments to the Second Edition

We wish to acknowledge those who have helped us in various ways during the preparation of the second edition of *Contemporary Oral and Maxillofacial Pathology*. Again, we are grateful to colleagues with whom we work on a daily basis. They provide continual moral support and meaningful suggestions that have lead to many substantial improvements in this text. Dr. Heddie O. Sedano has contributed multiple images and provided the genetic basis for many of the developmental and hereditary conditions. Dr. Russell E. Christensen has been most helpful and gracious with our shared material, and his suggestions have substantially added to the second edition. We also wish to acknowledge the insightful thoughts of Dr. Sotirios Tetradis during discussions related to basic mechanisms of bone cell differentiation.

We are sincerely appreciative of the Elsevier staff of Penny Rudolph, Executive Editor, and Kimberly Alvis, Senior Development Editor, who have patiently guided

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Developmental Disturbances of the Oral Region

CHAPTER OUTLINE

TEETH

- Disturbances in Size
 - Microdontia
 - Macrodontia
- Disturbances in Number
 - Total and Partial Anodontia
 - Supernumerary Teeth
- Disturbances in Eruption
 - Premature Eruption
 - Delayed Eruption
 - Impacted Teeth
 - Eruption Sequestrum
- Disturbances in Shape
 - Dilaceration
 - Taurodontism
 - Dens Invaginatus
 - Supernumerary Cusps
 - Supernumerary Roots
 - Gemination
 - Fusion
 - Concrescence
 - Hypercementosis
 - Cervical Enamel Projection
- Disturbances in Structure of Enamel
 - Acquired Disturbances
 - Amelogenesis Imperfecta
- Disturbances in Structure of Dentin
 - Dentinogenesis Imperfecta
 - Dentin Dysplasia
- Regional Odontodysplasia
- Disturbances in Structure of Cementum
 - Hypophosphatasia

SOFT TISSUE

- Congenital Lip Pits
- Double Lip
- Frenal Tag
- Ankyloglossia
- Macroglossia
- Fordyce Granules
- Leukoedema
- White Sponge Nevus
- Lingual Thyroid Nodule
- Oral Tonsil
- Retrocuspid Papilla

BONE

- Hemifacial Hypertrophy
- Hemifacial Atrophy
- Cleft Lip and Cleft Palate
- Lingual Mandibular Salivary Gland Depression
- Focal Osteoporotic Bone Marrow Defect
- Cleidocranial Dysplasia
- Crouzon Syndrome (Craniofacial Dysostosis)
- Treacher Collins Syndrome (Mandibulofacial Dysostosis)
- Down Syndrome (Trisomy 21)
- Oral-Facial-Digital Syndrome, Type I
- Papillon-Lefèvre Syndrome

ADDITIONAL KEY TERMS

- Fluoride mottling
- Hutchinson incisors
- Leong premolar
- Macrostomia
- Mesiodens
- Mulberry molars
- Natal teeth
- Neonatal teeth
- Paradental cyst
- Pulpal calcifications
- Romberg syndrome
- Turner tooth



Developmental disturbances of the oral region are discussed under three broad categories: (1) developmental disturbances affecting teeth, (2) developmental disturbances limited to soft tissue, and (3) developmental disturbances affecting bone.

TEETH

DISTURBANCES IN SIZE

Microdontia

MICRODONTIA: One or more teeth that are smaller than normal.

When all teeth in both arches are smaller than normal, the condition is termed *generalized microdontia*. If all the teeth are uniformly smaller than normal, which occurs in uncommon conditions such as pituitary dwarfism, the condition is termed *true generalized microdontia*. The term *relative generalized microdontia* is used when the mandible and maxilla are somewhat larger than normal but the teeth are of normal size, giving the illusion of generalized microdontia. In the latter, the teeth are spaced.

Microdontia involving one or two teeth is far more common than the generalized types. Individual teeth most frequently affected by microdontia are the maxillary lateral incisors (peg laterals) (Figure 1-1, A) and the maxillary third molars (Figure 1-1, B). In addition to being miniature teeth, the crowns often exhibit a conical shape. However, maxillary and mandibular second premolars, which are often congenitally absent, rarely exhibit microdontia. Supernumerary teeth are commonly smaller than normal, and their crowns are often conical.

Macrodonia

MACRODONTIA: One or more teeth that are larger than normal.

When all teeth in both arches are measurably larger than normal, the condition is termed *true generalized macrodonia* (seen in rare conditions such as pituitary gigantism). The term *relative generalized macrodonia* is used to describe a condition in which the mandible, the maxilla, or both are somewhat smaller than normal but the teeth are normal in size. In this condition the arches

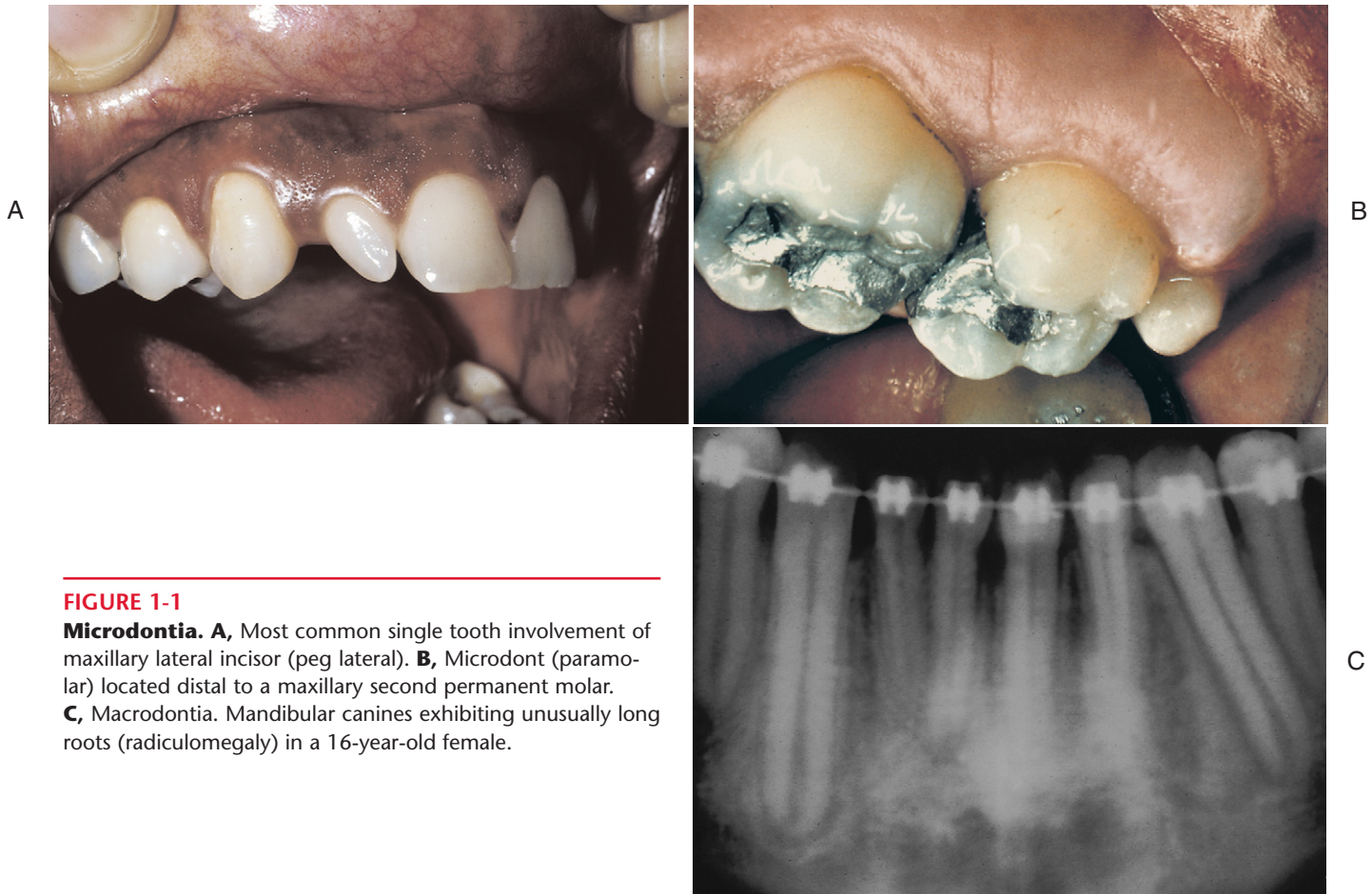


FIGURE 1-1

Microdontia. **A,** Most common single tooth involvement of maxillary lateral incisor (peg lateral). **B,** Microdont (paramolar) located distal to a maxillary second permanent molar. **C,** Macrodonia. Mandibular canines exhibiting unusually long roots (radiculomegaly) in a 16-year-old female.

exhibit crowding of teeth. Regional or localized macrodontia is occasionally seen on the affected side of the mouth in patients with hemifacial hypertrophy and in segmental odontomaxillary dysplasia. Macrodontia of an individual tooth is occasionally seen but is rare and should not be confused with the fusion of two adjacent teeth. Rhizomegaly, also termed *radiculomegaly*, is an uncommon type of macrodontia in which the root or roots of a tooth are considerably longer than normal. This condition most commonly affects the roots of the mandibular cuspid teeth (Figure 1-1, C).

DISTURBANCES IN NUMBER

Total and Partial Anodontia

TOTAL ANODONTIA: Congenital absence of all teeth.

PARTIAL ANODONTIA (HYPODONTIA): Congenital absence of one or more teeth.

Total anodontia is a rare condition in which the patient has no deciduous and no permanent teeth. It usually occurs in association with a generalized disorder

such as hereditary ectodermal dysplasia. Hypohidrotic ectodermal dysplasia is inherited as a genetic heterogeneity, in some families as an X-linked recessive disorder affecting essentially males, and in other families as an autosomal recessive disorder affecting males and females. The gene for the X-linked variety has been mapped to the long arm of the X chromosome (Xq12-q13.1). A gene from this region has been found to encode a transmembrane protein that is expressed in keratinocytes, hair follicles, and sweat glands. All features are basic to defects in the development of the ectodermally derived structures (hair, sweat glands, teeth). The hair may be absent or of the lanugo type (Figure 1-2, A), and the reduction or absence of sweat glands results in the inability to regulate body temperature. Although most cases of ectodermal dysplasia exhibit some congenitally absent teeth (hypodontia), total anodontia is rare. Even in the most severe cases of ectodermal dysplasia the cuspids and first molars are present, although they may exhibit anomalous crowns (Figure 1-2, B and C).

The more common form of anodontia is partial anodontia, also termed *hypodontia* or *oligodontia*, and involves one or more teeth (Figure 1-3). Although any tooth can be congenitally absent, certain teeth tend to

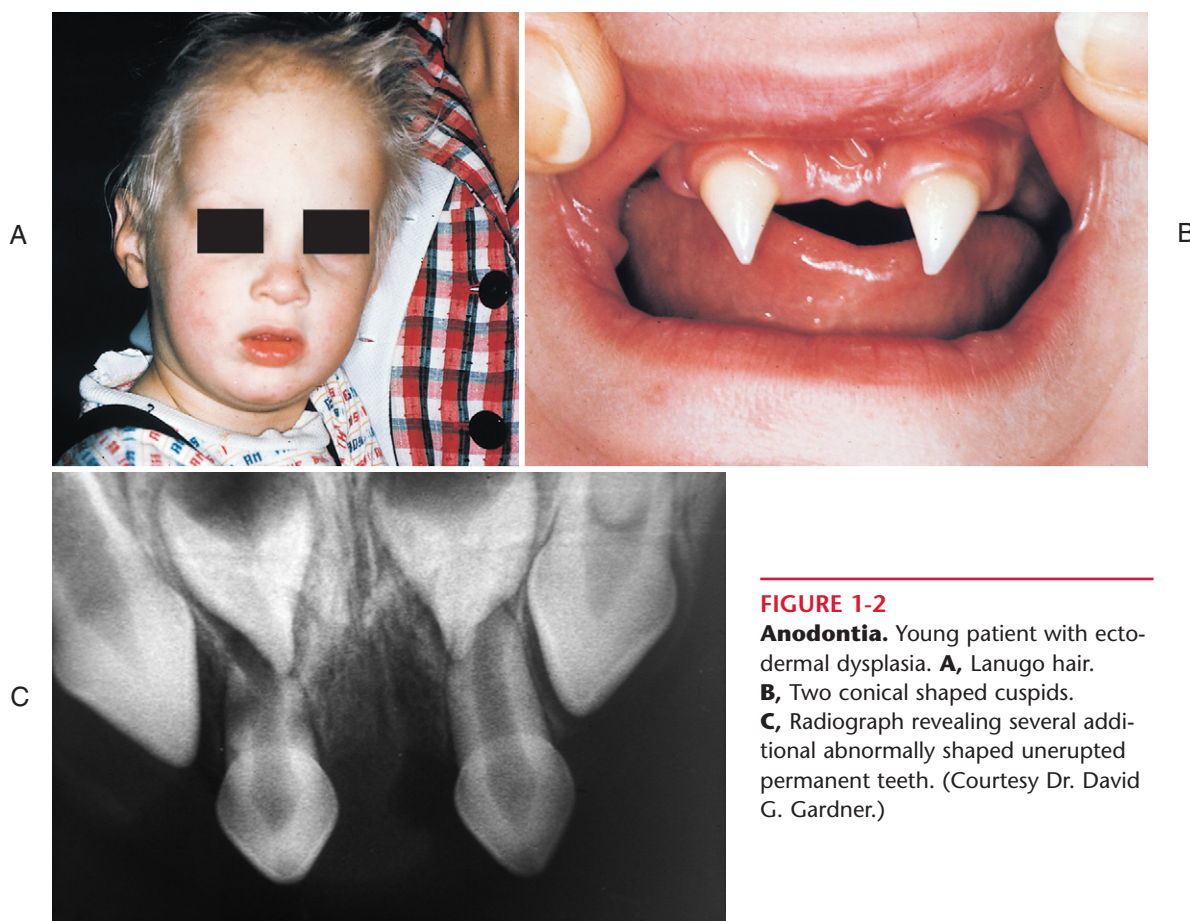


FIGURE 1-2

Anodontia. Young patient with ectodermal dysplasia. **A**, Lanugo hair. **B**, Two conical shaped cuspids. **C**, Radiograph revealing several additional abnormally shaped unerupted permanent teeth. (Courtesy Dr. David G. Gardner.)

be absent more often than others. The most common congenitally absent teeth are the third molars, followed by the maxillary lateral incisors and the second premolars. Although the percentage of congenitally absent teeth varies, as high as 35% of the general population has at least one congenitally absent third molar. Congenital absence of all third molars is common, but congenital absence of deciduous teeth is uncommon. When a deciduous tooth is congenitally absent, it is most often the maxillary lateral incisor. A close correlation exists between congenital absence of a deciduous tooth and congenital absence of the permanent successor, suggesting some genetic influence. Familial tendency for congenitally absent teeth is well recognized.



FIGURE 1-3

Hypodontia. Congenitally absent left maxillary central incisor resulting in underdevelopment of the maxilla and severe malocclusion.

Supernumerary Teeth

SUPERNUMERARY TEETH: *Teeth in excess of the normal number.*

Although these teeth can occur in any location, they have a predilection for certain sites. They are far more common in the maxilla (90%) than in the mandible (10%). A supernumerary tooth located between the maxillary central incisors, usually termed a **mesiodens** (Figure 1-4, A and B), is the most common, followed by maxillary fourth molars (paramolars) and maxillary lateral incisors. In the mandible the most common supernumerary teeth are premolars, although fourth molars and supernumerary incisors are also occasionally seen. A supernumerary tooth may resemble the corresponding normal tooth (Figure 1-5), or it may be rudimentary and bear little or no resemblance to its normal counterpart. The mesiodens and the paramolars often exhibit conical crowns; the latter are usually located on the buccal or palatal aspect of the normal maxillary molars. Supernumerary deciduous teeth are uncommon; however, when they do occur, the most common is a maxillary lateral incisor. Supernumerary teeth may be single or multiple and erupted or impacted. Multiple supernumerary teeth, which are generally impacted, are characteristically seen in cleidocranial dysplasia and Gardner syndrome.

DISTURBANCES IN ERUPTION

The eruption times for deciduous and permanent teeth are variable. It is therefore difficult to assess the eruption times for any given individual. Only when the eruption

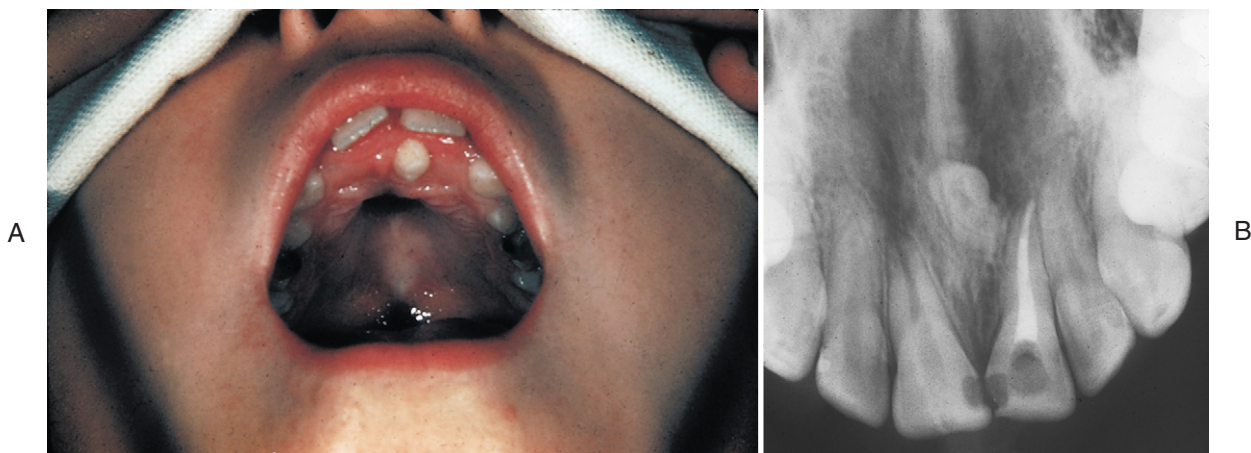


FIGURE 1-4

Supernumerary teeth. **A**, An erupted miniature conically shaped extra tooth is present in the midline of the anterior palate (mesiodens). **B**, A similarly located extra tooth that is impacted and unable to erupt.

time or sequence is obviously outside of the normal range can one consider that an eruption abnormality exists.

Premature Eruption

Erupted deciduous teeth present at birth are termed **natal teeth** (Figure 1-6). Deciduous teeth that erupt during the first 30 days of life are termed **neonatal teeth**. Premature eruption usually involves only one or two teeth, most commonly the deciduous mandibular central incisors. Although the cause of this phenomenon is unknown, a familial pattern is sometimes observed. Natal teeth and neonatal teeth are usually part of the normal complement of deciduous teeth; they are not supernumerary teeth and should therefore be retained if possible.

Premature eruption of permanent teeth is usually a consequence of premature loss of the preceding deciduous teeth. This becomes readily apparent when a single deciduous tooth has been prematurely lost. In the event that the entire permanent dentition is obviously erupting prematurely, the possibility of an endocrine dysfunction such as hyperthyroidism should be considered.

Delayed Eruption

Delayed eruption usually refers to the first appearance of deciduous teeth relative to the normal age range. This occurrence is relatively uncommon and is usually idiopathic or associated with certain systemic conditions such as rickets, cleidocranial dysplasia, or cretinism. Local factors such as gingival fibromatosis, in which dense fibrous connective tissue impedes tooth eruption, can result in delayed eruption of the deciduous dentition. Treatment of the systemic condition or the causative local factors may alleviate the eruption

problem. In conditions such as cleidocranial dysplasia, the pathophysiologic basis for noneruption is unclear and no known treatment exists. Delayed eruption of permanent teeth may result from the same local and systemic conditions that give rise to the delayed eruption of deciduous teeth.

Impacted Teeth

IMPACTED TEETH: Teeth with eruption that is impeded by a physical barrier.

Teeth that fail to erupt because of some physical barrier are termed *impacted teeth*. Examples of physical barriers that impair tooth eruption and result in impaction include dental crowding, supernumerary teeth, some odontogenic cysts, and odontogenic tumors (particularly odontomas). Although virtually any tooth can be impacted, the most common impacted teeth are the mandibular and maxillary third molars and maxillary cuspids, followed by the mandibular second premolars and supernumerary teeth. Impacted third molars have been classified according to their orientation within the dental arch, hence the terms *mesioangular*, *distoangular*, *horizontal*, and *vertical* impactions. Mesioangular impactions are the most common type. An impacted tooth that is totally surrounded by bone is considered to be completely impacted (Figure 1-7, A), whereas one that is partly in bone and partly in soft tissue is considered to be partially impacted (Figure 1-7, B).

Partially impacted teeth, particularly mandibular third molars, may communicate with the oral cavity via an inconspicuous periodontal pocket on the distal aspect of the adjacent second molar, thus predisposing the impacted tooth to pericoronal infection and dental caries. A tooth that is completely impacted does not



FIGURE 1-5
Supernumerary teeth. A fully developed normal extra premolar that has erupted lingually to the arch.



FIGURE 1-6
Natal teeth. Two normally sized mandibular incisors that were present at birth. (Courtesy Dr. Heddie O. Sedano.)

communicate with the oral cavity and is therefore not vulnerable to infection or dental caries. Individual teeth that fail to erupt for no apparent reason have sometimes been termed *embedded teeth*; however, this term is rarely used (Figure 1-7, C). Instead, all examples of delayed eruption are collectively termed *impacted teeth*.

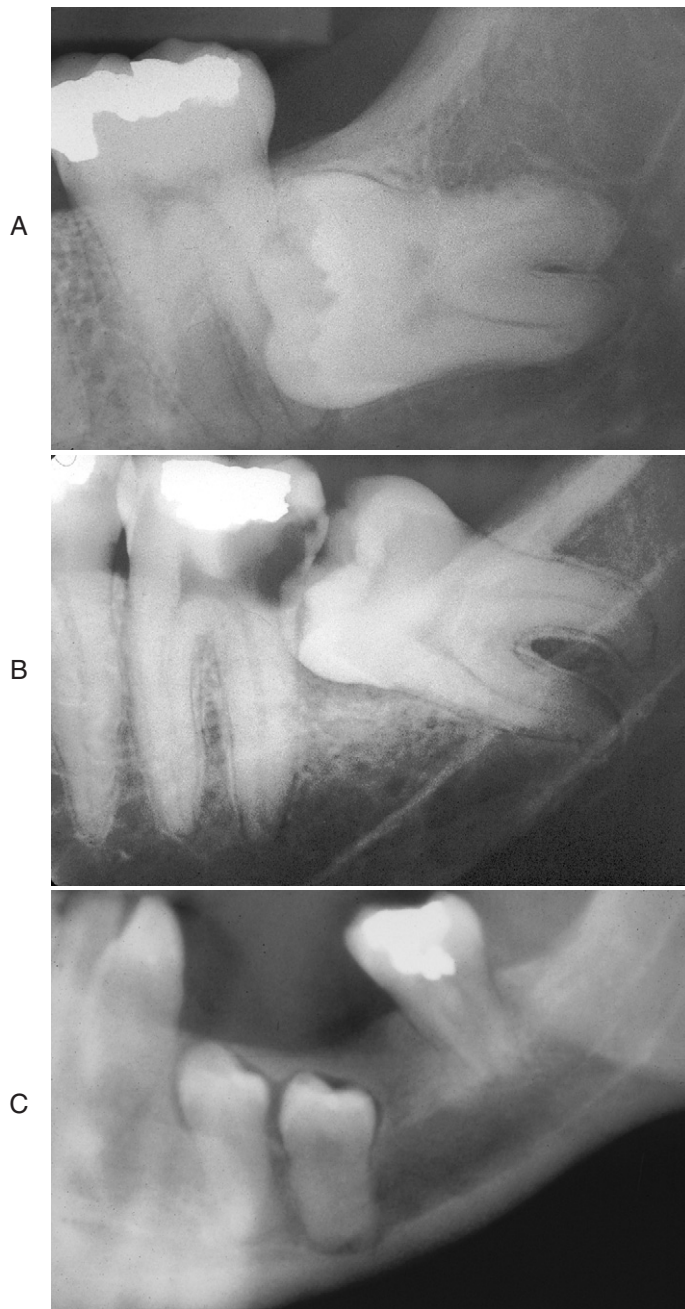


FIGURE 1-7

Impacted teeth. Completely (A) and partially impacted (B) mandibular third molars. A large area of dental caries is present on the distal aspect of the adjacent molar tooth. C, Vertically impacted (embedded) premolar teeth.

The common complications of impacted teeth are root resorption of adjacent normal teeth, infection and associated pain, a predisposition to dentigerous cyst formation, and external resorption of the impacted tooth. External resorption in an impacted tooth usually begins in the occlusal area of the crown and radiographically resembles dental caries. The treatment of impacted teeth will vary with the involved tooth and the individual circumstances. Most impacted molars are surgically removed. Because the maxillary cuspids are important cornerstones in the maxillary dentition, special efforts are usually made to retain these teeth. To accomplish this, the crown of the impacted maxillary cuspid is first surgically uncovered; then, with the aid of an orthodontic appliance, the tooth is slowly guided into its proper position in the dental arch. When a physical barrier such as a cyst, tumor, or supernumerary tooth causes tooth impaction, the treatment must include the removal of the causative barrier; whether the impacted tooth is also removed at the same time will depend on individual circumstances.

Eruption Sequestrum

ERUPTION SEQUESTRUM: A small spicule of calcified tissue that is extruded through the alveolar mucosa that overlies an erupting molar.

An eruption sequestrum may arise from the small area of slightly thickened cortical bone that occupies the area of the central occlusal fossa of molars or may represent a miniature complex odontoma present in the follicular soft tissue overlying the tooth. As a molar erupts through bone into the alveolar soft tissue, bone resorption over the cusps is completed ahead of the

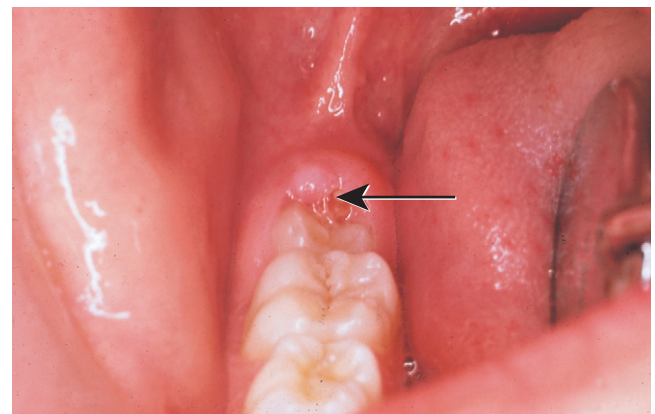


FIGURE 1-8

Eruption sequestrum. A small spicule of hard tissue, usually a tiny complex odontoma or a fragment of nonvital bone, is present on the occlusal fossa of the third molar (arrow).

resorption over the central depression of the crown (the *occlusal fossa*). The net result is a small island of nonvital bone or odontoma that is pushed out ahead and above the erupting molar (Figure 1-8). Although most eruption sequestra are spontaneously exfoliated and therefore require no treatment, they may occasionally remain in the alveolar mucosa for several days and may be brought to the attention of a dentist. In this event, they can be easily removed.

DISTURBANCES IN SHAPE

Dilaceration

DILACERATION: A sharp bend or angulation involving the root of a tooth.

Although occasional examples of dilaceration result from trauma during tooth development (Figure 1-9, A and B), most cases are the result of continued root formation during a curved or tortuous path of eruption. In some instances the cause of the bent or curved root is idiopathic (Figure 1-9, C). Dilaceration

can complicate tooth extraction, underlining the importance of securing preoperative radiographs before extracting a tooth (Figure 1-9, D).

Taurodontism

TAURODONTISM: A molar with an elongated crown and apically placed furcation of the roots, resulting in an enlarged rectangular coronal pulpal chamber.

Taurodontism, meaning *bull-like* teeth, is a developmental disturbance that primarily affects molars, although premolars are also occasionally affected. Both the permanent and deciduous teeth may be affected, although involvement of the permanent teeth appears to be more common. The condition is readily recognized radiographically and characterized by teeth that exhibit an overall rectangular shape, minimal constriction and definition of the cervical margin, and an apically displaced furcation that results in an extremely large pulpal chamber that exhibits an exaggerated apical-occlusal height and short pulpal canals (Figure 1-10, A and B). The unusual root shape probably results from

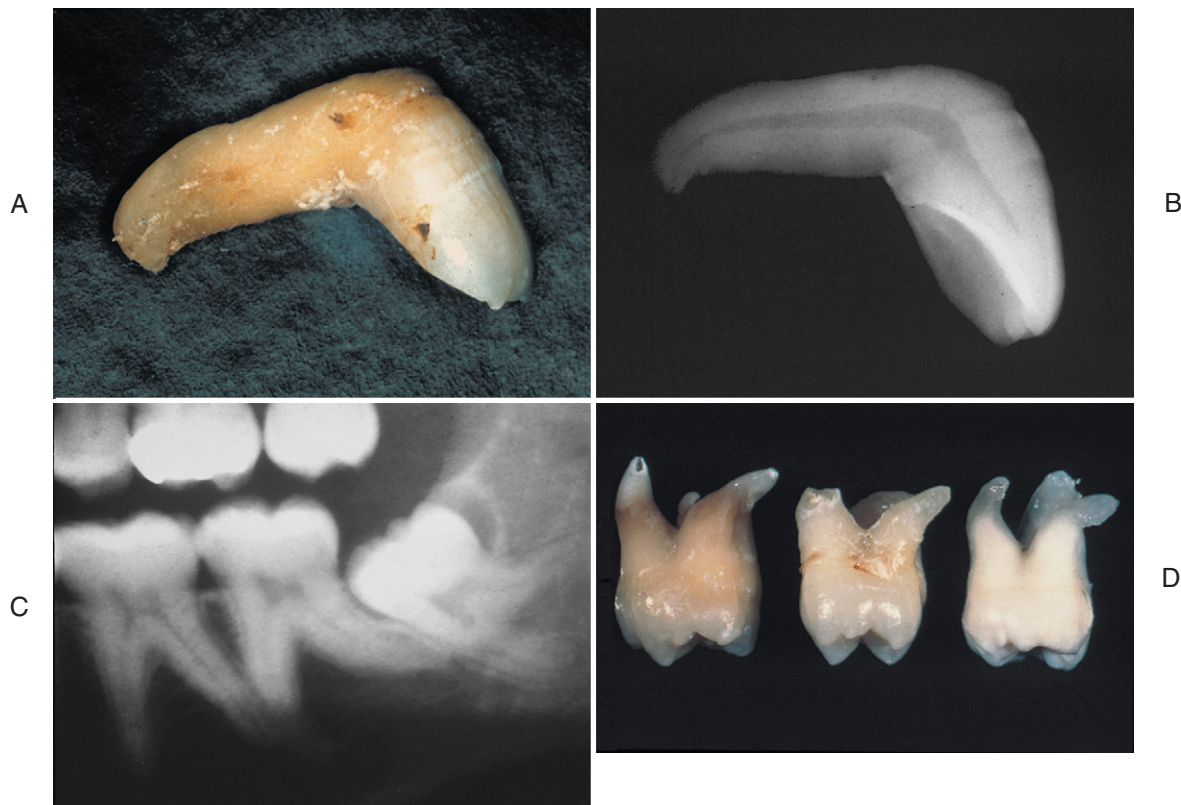
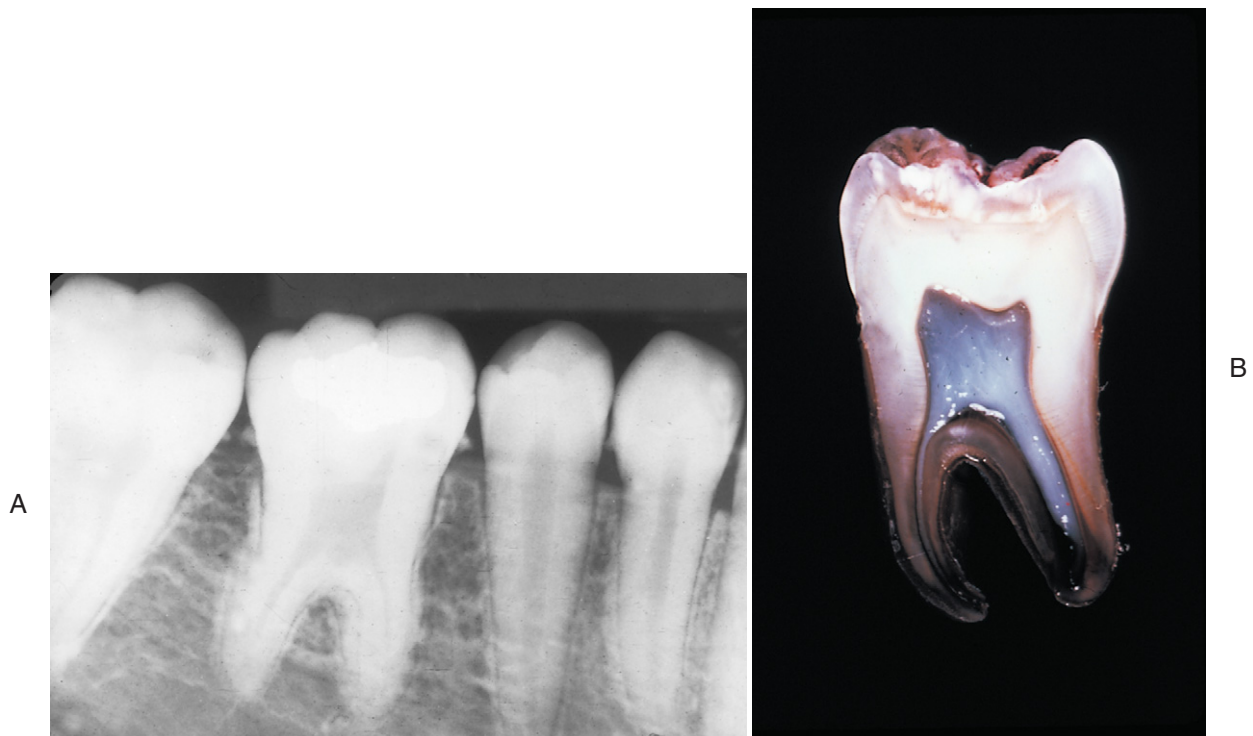


FIGURE 1-9

A, Dilaceration of a maxillary central incisor that prevented the eruption of the tooth. **B**, Radiograph of the dilacerated maxillary central incisor reveals the bend in the pulp canal. **C**, Dilacerated roots of the second and third molars. **D**, Dilacerated roots of extracted maxillary molars.

**FIGURE 1-10**

Taurodontism. **A**, Radiograph of a molar with an enlarged coronal pulpal chamber and lowered bifurcation area of roots. **B**, Similar abnormally formed tooth that has been cut in a sagittal plane to illustrate the abnormal shape of the tooth and its pulpal chamber.

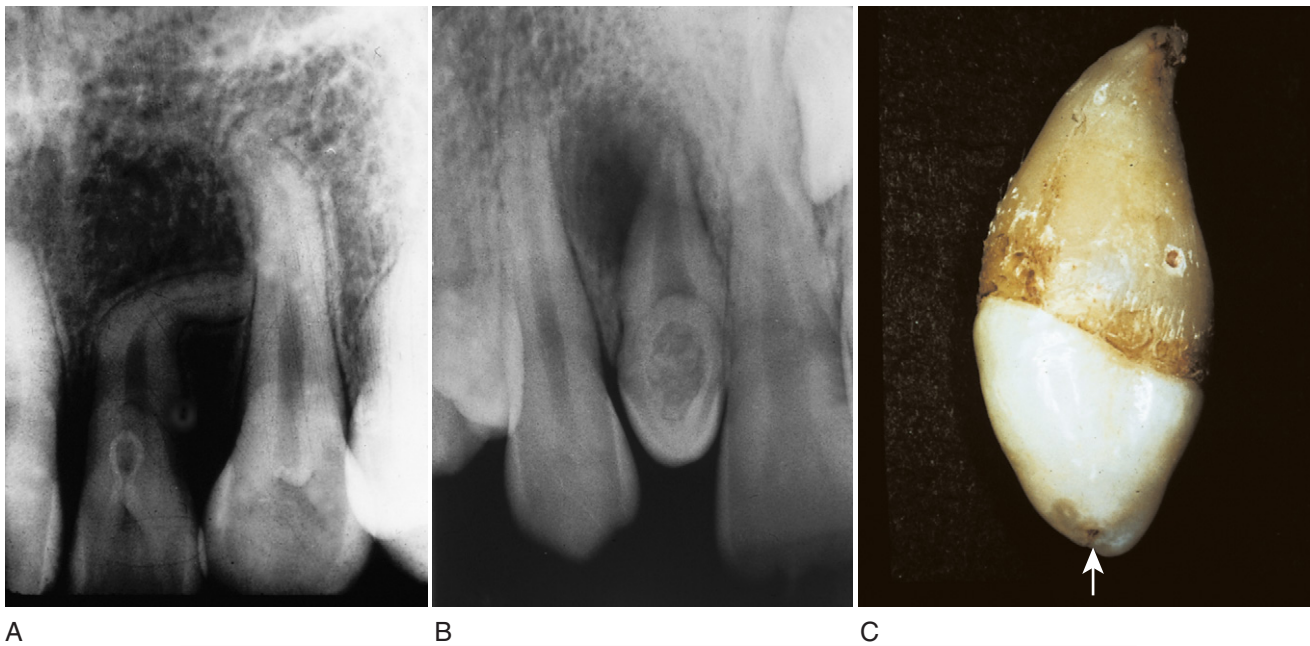
late invagination of Hertwig's root sheath, the mechanism that determines the shape of the tooth roots. Taurodontism may also occur in patients with amelogenesis imperfecta, Klinefelter syndrome, and Down syndrome. Of anthropologic interest is the fact that taurodontism was relatively common in Neanderthal man and thus may be a form of *atavism*, the occurrence of ancestral forms. Taurodontism requires no treatment but can be a complicating factor during root canal treatment procedures.

Dens Invaginatus

DENS INVAGINATUS: A developmental dental anomaly characterized by a deep enamel-lined pit that extends for varying depths into the underlying dentin, often displacing the pulp chamber and sometimes altering (expanding) the shape of the root.

Dens invaginatus, also termed *dens in dente*, is a developmental abnormality that primarily affects the permanent maxillary lateral incisors; however, maxillary central incisors and other teeth can also be occasionally affected. A mild form of this anomaly is relatively com-

mon and is characterized by the presence of an invaginated lingual pit that extends for varying distances into the substance of the tooth. The extent of the invagination is not always clinically visible. The external pit on the lingual surface is often inconspicuous on clinical examination but may be visible in a periapical radiograph (Figure 1-11, A to C). In most cases of dens invaginatus, the pit on the enamel surface is located on the lingual aspect of the incisor tooth, however, cases that involve peg-shaped lateral incisors usually exhibit the pit at the tip of the conical crown. A radiograph is helpful in establishing the diagnosis. In its most extreme form the deep invagination results in a bulbous expansion of the affected root, a form that has been erroneously termed a *dilated odontoma* (Figure 1-12). The base of the pit or deep invagination is composed of a thin, often defective layer of enamel and dentin that is extremely vulnerable to carious destruction soon after the tooth erupts into the oral cavity (Figure 1-13). As a result, most teeth with deep invaginations quickly develop pulpitis, pulpal necrosis, and inflammatory periapical disease in what clinically appears to be an intact tooth. Because of their altered structure, these teeth are seldom reliable candidates for successful endodontic

**FIGURE 1-11**

Dens invaginatus. Radiograph of lateral incisors exhibiting a mild form of the defect in a tooth with a dilaceration of the root (**A**) and a moderate form in which the tooth is conically shaped and exhibits the characteristic appearance of a tooth within a tooth (dens in dente) (**B**). Both teeth have the commonly associated periapical lesions. **C**, Gross appearance of the dens in dente form of the anomaly with the small orifice visible at the tip of the crown (arrow).

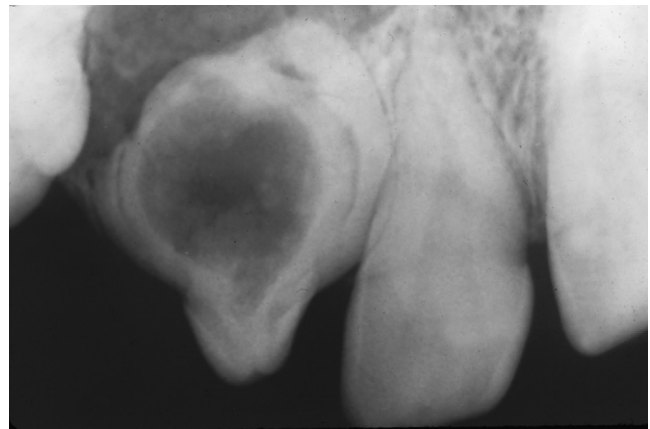
treatment. For the deep lingual pits in otherwise normally shaped teeth, early radiologic diagnosis and prophylactic restorative treatment of the abnormality are essential if pulpal and periapical diseases are to be prevented. Treatment of the more severe forms of dens invaginatus is usually extraction.

Supernumerary Cusps

Occasionally, teeth exhibit additional or supernumerary cusps. The most common example of this phenomenon is the Carabelli cusp, which typically develops on the mesiolingual surface of permanent maxillary first molars. This particular supernumerary cusp usually presents no clinical problems and is therefore considered to simply represent a normal anatomic variation. Occasionally, however, certain teeth exhibit supernumerary cusps that result in clinical problems that may require treatment. Examples of such supernumerary cusps are dens evaginatus and talon cusps.

Dens evaginatus

DENS EVAGINATUS: A developmental anomaly characterized by a cusplike supernumerary focal enamel protrusion on the occlusal or lingual surface of the crown.

**FIGURE 1-12**

Dens invaginatus. Radiograph of the most severe form of this anomaly, revealing a large, bulbous expansion of the root portion and a central radiolucency. This form is sometimes termed *dilated odontoma*.

Dens evaginatus is a developmental abnormality that primarily affects premolar teeth. It is characterized by the development of an abnormal globe-shaped projection of enamel in the region of the central groove, between the buccal and lingual cusps of premolars, although any tooth

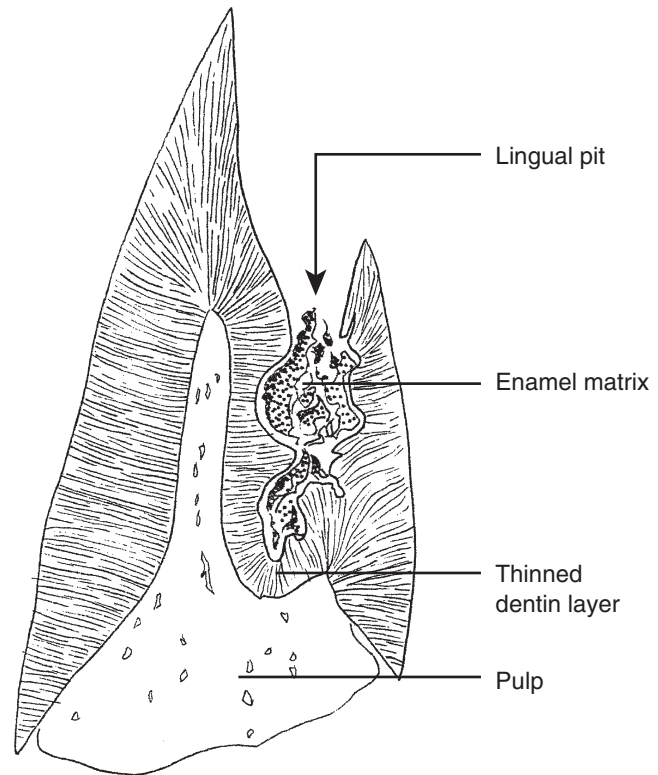
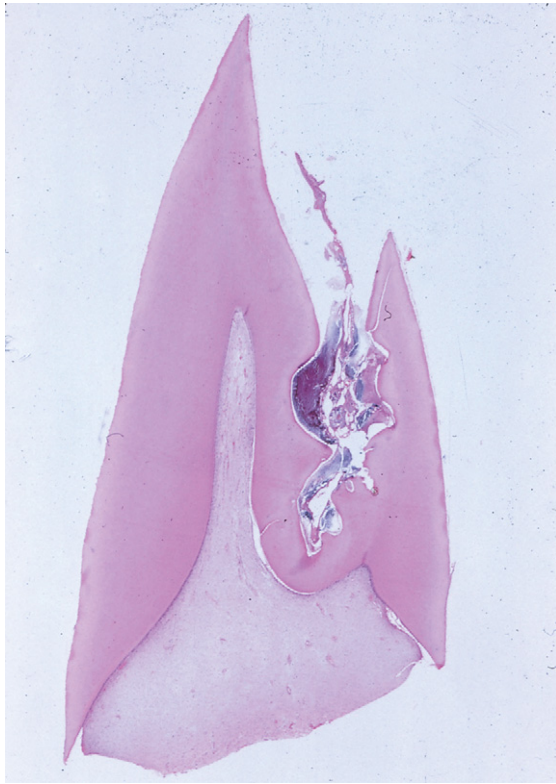


FIGURE 1-13

Dens invaginatus. Photomicrograph of a decalcified section of a developing tooth with a deep lingual pit. A thin layer of dentin separates the base of the invagination from the pulp.

may be involved (Figures 1-14, A and B, and 1-15, A and B). It commonly occurs in Chinese, Japanese, Filipino, Northern Native, and American Indian patients and occasionally in patients of Northern European heritage (white). In Singapore and Malaysia, this anomaly is popularly referred to as **Leong premolar**, after M.O. Leong, who first drew attention to this entity in 1946. The clinical significance of dens evaginatus is that it can interfere with tooth eruption and result in incomplete eruption or tooth displacement. Because this extra cusp contains a pulp horn, attrition or fracture can result in pulp exposure leading to pulpal inflammation and its sequelae. As with any type of supernumerary cusp, the dentist should be aware that it usually contains a pulp horn that can be readily exposed as a result of functional attrition or if mechanical reduction or removal of the cusp is attempted.

Talon cusp

An uncommon but clinically significant form of supernumerary cusp, typically seen on the lingual aspect of maxillary central incisors, is called a *talon cusp*, because its unusual shape resembles an eagle's talon. This ab-

normal cusp arises from the cingulum portion of the tooth and usually extends to the incisal edge as a prominent projection of enamel that imparts a T shape (Figure 1-16). Occasionally, deep lingual pits develop on either side of the talon cusp, where it joins the lingual surface of the tooth. If lingual pits are present, these should be restored to prevent dental caries. If the cusp interferes with normal occlusion, preventive care that includes endodontic and restorative treatment of the affected tooth may be required to achieve normal tooth form. Simple reduction of the cusp should not be attempted, because the cusp contains a prominent pulp horn; therefore pulp exposure is almost certain to occur. Although this abnormality is uncommon in the general population, it has been reported to be more prevalent in patients with Rubinstein-Taybi syndrome.

Supernumerary Roots

Additional roots (more than the expected number) are termed *supernumerary roots*. This is a common developmental phenomenon that is most often seen in

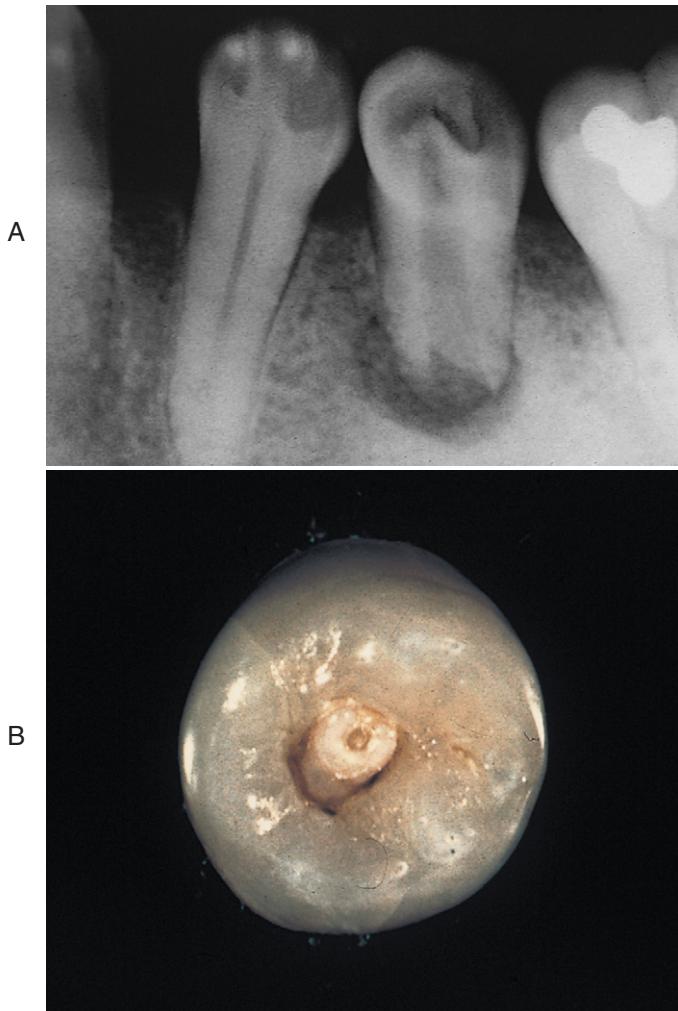
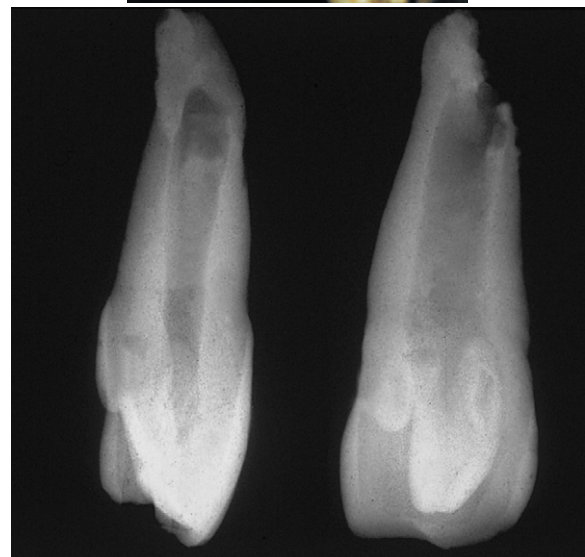


FIGURE 1-14

A, Mandibular first and second premolar teeth exhibiting dens evaginatus in a 36-year-old Asian male. The second premolar is nonvital as a result of an attrition-induced pulp exposure. The nonvital premolar was extracted. **B**, Occlusal view of the dens evaginatus in the extracted premolar tooth. The reader should note the pinpoint area of attrition at the tip of the dens evaginatus.



A



B

FIGURE 1-15

Dens evaginatus. **A**, Maxillary central incisor exhibiting a large and a small cuspal projection on the lingual surface. **B**, Dens in dente adjacent to a supernumerary lingual cusp in a maxillary central incisor.

FIGURE 1-16

Talon cusp. In this specific form of dens evaginatus, cuspal projections are present bilaterally and arise from the gingulum of the lateral incisors, resembling eagle's talons.

mandibular premolars (Figure 1-17), cuspids, and maxillary and mandibular third molars. Before dental extractions or endodontic treatment are undertaken, it is important to radiologically image the teeth to identify any supernumerary roots and thereby facilitate appropriate treatment planning.



FIGURE 1-17
Supernumerary roots. Maxillary premolar with three roots rather than the usual two.

Gemination

GEMINATION: A developmental dental anomaly characterized by a single-rooted tooth with either an unusually wide, partly-divided crown or two separate crowns; thought to represent the result of an incompletely divided tooth germ.

Gemination is a developmental anomaly that primarily affects anterior teeth and that clinically resembles another anomaly known as *fusion*. Although they are clinically and microscopically similar, they result from two different developmental processes. Gemination is characterized by the partial division or twinning of a single tooth germ, resulting in a tooth that exhibits two separate or partly separated crowns and a single root and root canal (Figure 1-18, A). Gemination can affect the deciduous and permanent dentitions (Figure 1-18, B).

Fusion

FUSION: A developmental dental anomaly characterized by an abnormally shaped tooth that may exhibit an unusually wide crown, a normal crown with an additional root, or other combinations that result from the union of two adjacent tooth germs united by a common dentin.

Fusion is defined as the union of two normally separate tooth germs. The minimal criterion for fusion is that the teeth in question exhibit confluent dentin.

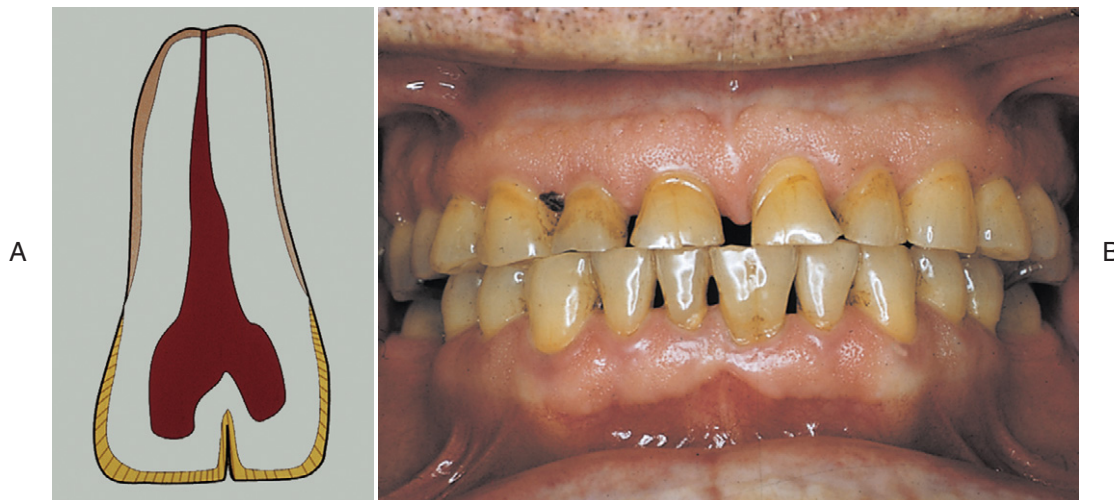


FIGURE 1-18

Gemination and fusion. **A**, Diagram of section through a tooth showing both gemination and fusion. Both may have the same microscopic appearance of a widened crown with common dentin, root, and pulpal chambers. Although both may have the same result, gemination occurs because of the partial splitting of a single tooth bud, whereas fusion results from the mingling of two adjacent tooth buds. **B**, Gemination. The patient exhibits an extra wide lower central incisor that is most likely caused by gemination, because a normal number of incisors are found in the arch.

**FIGURE 1-19**

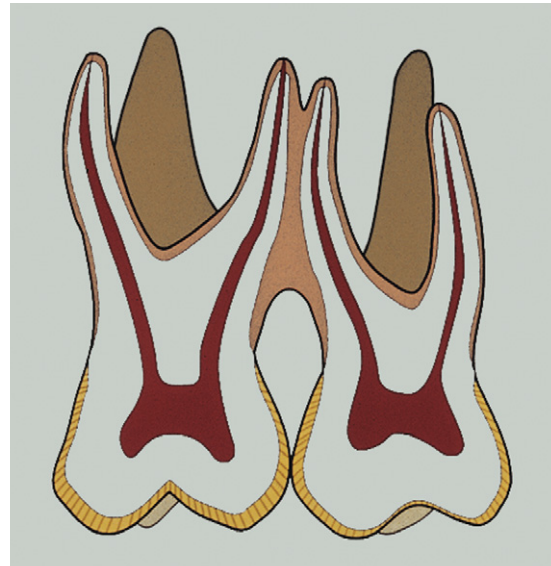
Fusion. Patient with an extra wide lower incisor most likely caused by fusion, because the arch contains three incisors instead of four.

This developmental condition can occur in the deciduous and permanent dentition. Some hereditary tendency has been reported. Fusion can be complete or incomplete, and its extent will vary with the stage of development that a tooth has reached at the time of fusion. If fusion begins before calcification, then the union will involve all components of the tooth, including enamel, dentin, cementum, and pulp. If the union begins at a later stage of tooth development, then the affected teeth may have separate crowns and the fusion may be limited to the roots. The pulp canals may be either fused or separate. Fusion can be differentiated from gemination by counting the teeth in the area. In the case of fusion, there will be one less tooth present in the arch (Figure 1-19). The clinical implications of fusion include esthetic considerations, crowding when fused to a supernumerary tooth, and periodontal disease.

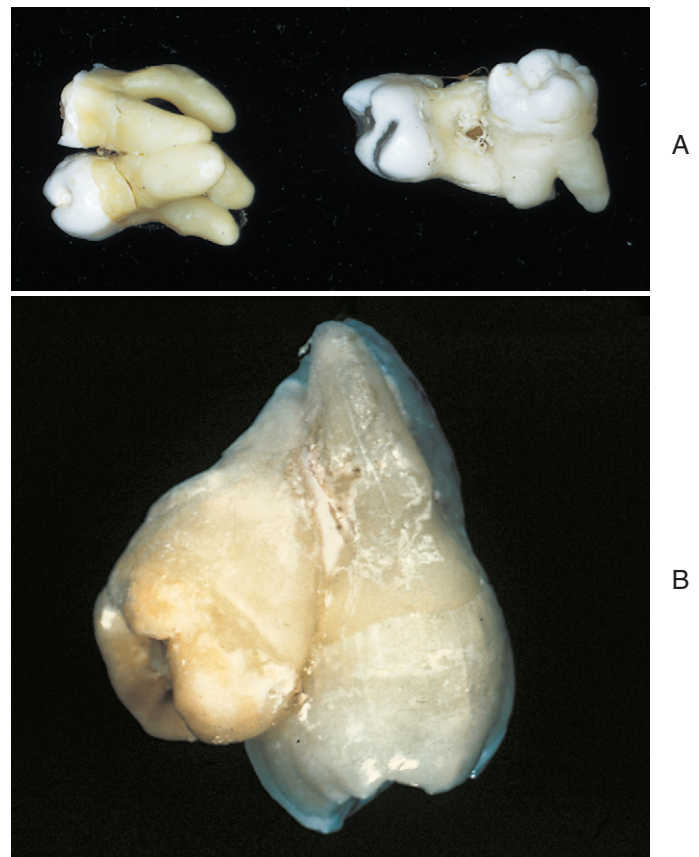
Concrescence

CONCRESCENCE: Union of the roots of two or more normal teeth caused by confluence of their cementum.

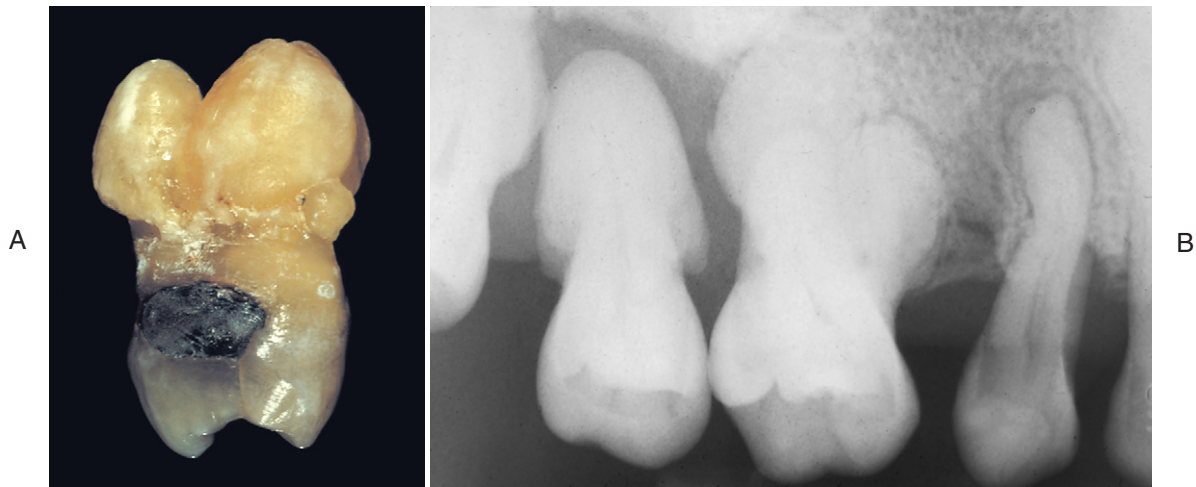
Concrescence is a type of fusion that occurs after root formation is complete. Union of the teeth is limited to and is the result of confluent cementum (Figure 1-20 and Figure 1-21, A and B). The condition is thought to occur as a result of traumatic injury to the area or crowding with interseptal bone loss, resulting in close approximation of the tooth roots. Concrescence can occur before or after tooth eruption and primarily involves the permanent maxillary molars. With rare exceptions, this

**FIGURE 1-20**

Concrescence. The union of two molars because of confluence of the cementum of the roots of two adjacent teeth.

**FIGURE 1-21**

Concrescence. **A**, Molars adhered to each other by fusion of their cementum. **B**, Concrescence involving maxillary second and third molars.

**FIGURE 1-22**

Hypercementosis. **A**, Maxillary molar exhibiting massive deposits of cementum on all roots. **B**, Radiograph of maxillary molars in an area of chronic inflammation exhibiting extensive hypercementosis.

type of union involves only two teeth. The clinical implications of concrescence relate primarily to the importance of its radiographic diagnosis before attempting tooth extraction. Failure to recognize its presence can result in the extraction of two teeth when a single extraction was intended.

Hypercementosis

Occasionally, one or more teeth exhibit excessive deposits of cementum on the root. Such deposits are sometimes problematic, because the apical portion of the root may have a larger diameter than the coronal portion, resulting in a bulbous or pear-shaped root (Figure 1-22, *A* and *B*). Teeth with these shapes are difficult to extract without surgically removing significant amounts of the surrounding bone.

Hypercementosis is more common in teeth that are subjected to either increased or decreased occlusal forces, on the teeth of patients with Paget disease or hyperpituitarism, and on adjacent teeth in areas of chronic inflammation. In teeth associated with periapical inflammatory lesions, the increased cementum commonly deposits in a band around the apical third of the root, with the root tip often exhibiting some resorption. Occasionally, adjacent teeth in an area of chronic inflammation may produce excessive cementum deposits on their roots that eventually fuse at those points, resulting in a concrescence. Because these changes are clinically undetectable, radiographic evaluation is a valuable aid before tooth extraction.

Cervical Enamel Projection

Focal apical extensions of the coronal enamel beyond the normally smooth cervical margin (cemento-enamel junction) and onto the root of the tooth are termed *cervical enamel projections* (Figure 1-23). These enamel pro-

**FIGURE 1-23**

Cervical enamel projection in a mandibular first permanent molar. The roots of the tooth have been stained with eosin to accentuate the cemento-enamel interface.

**FIGURE 1-24**

Enamelomas (enamel pearls) in extracted maxillary molars. **A**, These teeth also exhibit tetracycline staining. **B**, Large ectopic enamel projection in furcation area that may contain dentin and pulpal tissue.

jections are approximately 1 mm wide, 1 to 3 mm long, and occur primarily on maxillary and mandibular molars. Their clinical significance relates to the fact that they could contribute to periodontal pocket formation, which might progress to periodontal disease. The cervical enamel projection is also thought to play a role in the development of the **paradental cyst** (also referred to as *buccal bifurcation cyst* and *Craig cyst*). Cervical enamel projections differ from the ectopic droplets of enamel that primarily occur in the bifurcation or trifurcation areas on the roots of molars (Figure 1-24, A and B). These are termed *enamel pearls* or *enamelomas*. Enamel pearls are relatively uncommon and can be radiographically seen as 1 to 3 mm round radiopacities. Histologically, enamel pearls may be composed largely of enamel, or they may exhibit a central core of dentin. Treatment is not recommended, because it often leads to the development of root caries, external resorption, or pulpitis.

DISTURBANCES IN STRUCTURE OF ENAMEL

Acquired Disturbances

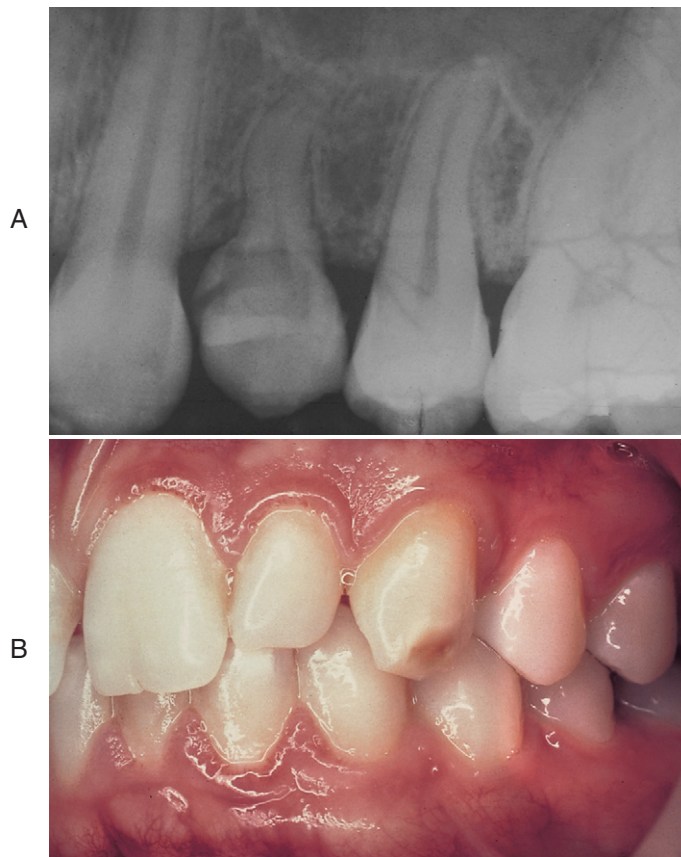
Disturbances in the structure of enamel can occur as a result of environmental or hereditary factors. Among the environmental factors are bacterial and viral infections (e.g., syphilis, scarlet fever), inflammation, nutritional deficiencies (e.g., vitamins A, C, D; calcium),

chemical injuries (e.g., fluoride), and trauma. Depending on the causative factor, the enamel disturbance may be localized to one or two teeth (focal), or it may affect many or all teeth (generalized). The extent of the enamel defect is generally related to the specific causative factor, the duration of the injury, and the stage of enamel formation at the time of the injury.

Enamel defects resulting from environmental factors usually affect either the deciduous or the permanent dentition but seldom both. Unlike hereditary factors that usually affect either the enamel or the dentin, environmental factors often damage both types of hard tissues.

Focal enamel hypoplasia

Localized or focal enamel hypoplasia involving only one or two teeth is relatively common. Although the cause is often unclear (idiopathic), in some cases it is readily apparent. A common form of focal enamel hypoplasia of known cause is **Turner tooth**, which results from localized inflammation or trauma during tooth development. Typical examples of this phenomenon occur when a deciduous tooth develops a caries- or trauma-related abscess that damages the underlying developing permanent successor (Figure 1-25, A). Depending on the severity of the injury, the affected crown may have an area of enamel hypoplasia that is relatively smooth with pitted areas or is grossly deformed with a yellowish or brownish discoloration (Figure 1-25, B).

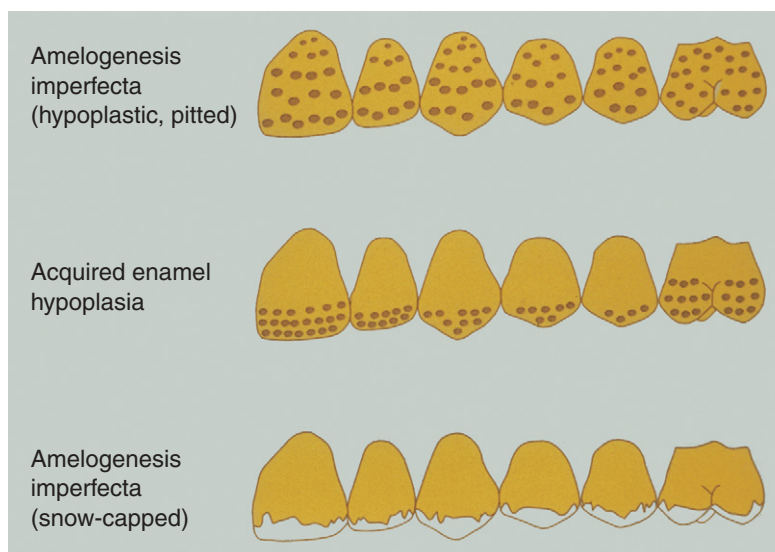
**FIGURE 1-25**

Turner tooth. **A**, Radiograph of first maxillary premolar exhibiting radiolucency as the result of hypoplasia acquired during development of the crown. **B**, Maxillary cuspid exhibiting an area of enamel hypoplasia (*brown discoloration*).

Generalized enamel hypoplasia

Short-term systemic environmental factors inhibit functioning ameloblasts at a specific period during tooth development and are manifested clinically as a horizontal line of small pits or grooves on the enamel surface that correspond to the time of development and the duration of the insult (Figure 1-26). If the duration of the environmental insult is brief, the line of hypoplasia is narrow, whereas a prolonged insult produces a wider zone of hypoplasia and may affect more teeth (Figure 1-27, A and B). Knowledge of the chronologic order of tooth development is helpful in determining the approximate time of an injurious insult. Clinical studies indicate that most cases of generalized environmental hypoplasia involve teeth that are formed in infants during the first year of life; thus the teeth that are most often involved are the permanent incisors, cuspids, and first molars. Premolars, second molars, and third molars are seldom affected, because their formation does not begin until a child is 3 years of age or older.

The enamel hypoplasia resulting from congenital syphilis affects the incisal edges of the permanent incisors (Figure 1-28) and the occlusal surfaces of the permanent first molars. The notched, screwdriver-shaped incisors are termed **Hutchinson incisors**, whereas the globular occlusal surfaces of the first molars are termed **mulberry molars**. Not all patients with congenital syphilis exhibit the hypoplastic changes previously described. In addition, occasional patients who have no history of congenital syphilis exhibit changes that are indistinguishable from mulberry molars and Hutchinson incisors. A diagnosis of congenital syphilis should

**FIGURE 1-26**

Acquired and hereditary enamel defects. Comparison of surface appearances of common enamel defects. The acquired type differs from the hereditary pitted hypoplastic type, because the defective enamel is limited to the portions of the teeth that were forming at the time of the insult.

**FIGURE 1-27**

Acquired enamel hypoplasia. **A**, Maxillary central incisors with a mild form of pitted enamel. **B**, Multiple teeth with horizontal band of severe form of enamel hypoplasia.

therefore be made only after conclusive evidence is available.

Enamel hypoplasia that results from hypocalcemia secondary to vitamin D deficiency is usually of the pitted type. It is clinically indistinguishable from enamel hypoplasia caused by exanthematous diseases such as measles, chicken pox, and scarlet fever and by vitamin A and C deficiencies.

The neonatal line that can be seen microscopically in nondecalcified ground sections of deciduous teeth and first permanent molars can be considered a mild form of enamel hypoplasia and is indicative of the systemic insult to the teeth during birth. Clinical studies also indicate that enamel hypoplasia is more common in prematurely born children than in those born at normal term.

A well-recognized example of chemically induced generalized enamel hypoplasia results from the ingestion of fluoride. Although total fluoride intake will vary with total water consumption, fluoride-induced enamel hypoplasia (**fluoride mottling**) is usually inconspicuous at levels below 1.0 ppm in the drinking water. With increased amounts of fluoride in the drinking water, the resultant enamel hypoplasia becomes progressively evi-

**FIGURE 1-28**

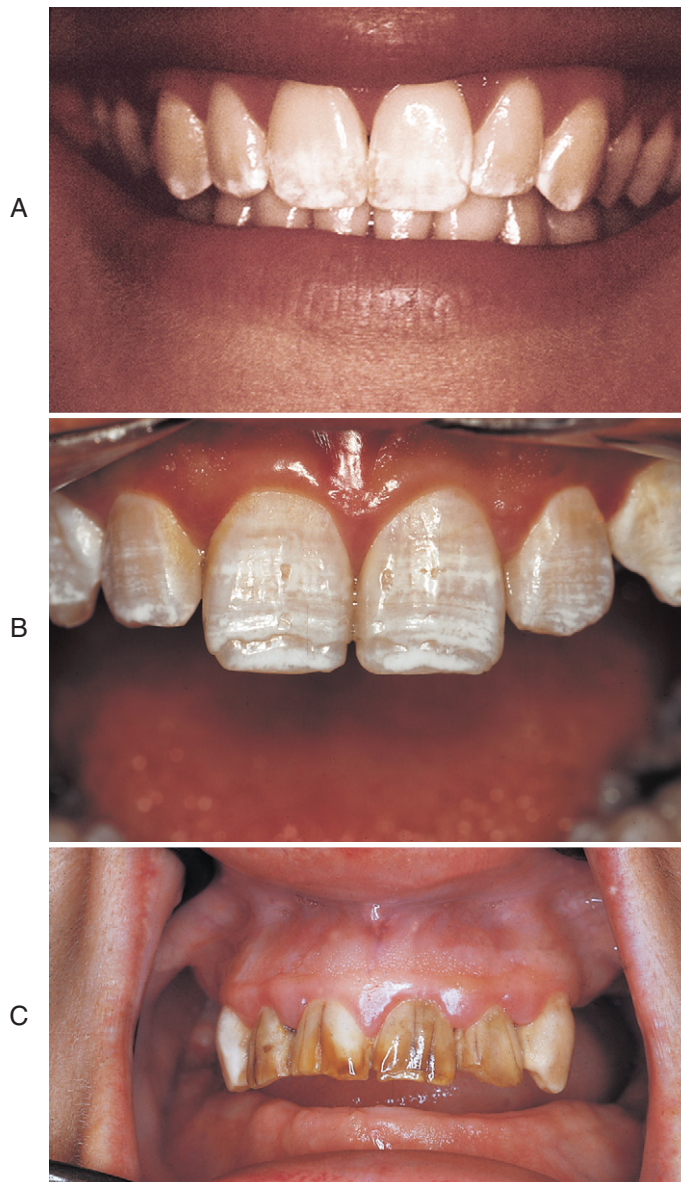
Acquired enamel hypoplasia. Severe generalized form of enamel hypoplasia caused by congenital syphilis. The teeth lack the formation of the central lobe of the crown, resulting in the screwdriver shape of the incisors.

dent. Increased fluoride levels interfere with ameloblastic function, which adversely affects both enamel matrix formation and enamel matrix calcification. Clinically, minimal fluoride mottling exhibits a smooth enamel surface with occasional subtle whitish flecking; mild mottling exhibits a smooth enamel surface with opaque white areas (Figure 1-29, A); moderate-to-severe mottling exhibits varying degrees of obvious pitting and brownish discoloration of the enamel surface (Figure 1-29, B). In severe fluoride mottling the enamel is considerably softer and weaker than normal, resulting in excessive wear and fracturing of the incisal and occlusal surfaces (Figure 1-29, C); conventional restorations are therefore difficult to retain. Regardless of the degree of fluoride mottling, affected teeth are largely resistant to dental caries.

Amelogenesis Imperfecta

AMELOGENESIS IMPERFECTA: A heterogeneous group of genetic disorders exhibiting faulty enamel formation.

Amelogenesis imperfecta is a heterogeneous group of hereditary disorders of enamel formation affecting both the primary and permanent dentitions. These disorders are confined to the enamel; the other components of the teeth are normal. Normal enamel formation progresses through three stages: (1) enamel matrix formation (functioning ameloblasts), (2) mineralization of the enamel matrix (primary mineralization), and (3) enamel maturation (secondary mineralization). Three basic types of amelogenesis imperfecta correlate with defects in these stages: (1) the *hypoplastic* type (focal or generalized), which exhibits decreased enamel matrix formation caused by a disturbance in the functioning of the ameloblasts; (2) the *hypocalcified* type, which exhibits a severe defect in

**FIGURE 1-29**

Fluorosis. **A,** Mild form of fluoride mottling, exhibiting white opaque flecks near the incisal edges with the surface remaining smooth and intact. **B,** Moderate form of fluoride mottling with ridges of hypoplasia and white and brownish enamel. **C,** Severe form of fluoride-induced hypoplasia and discoloration with associated cracking and chipping of the enamel.

mineralization of the enamel matrix; and (3) the *hypomaturation* type, which exhibits a less severe alteration in mineralization with focal or generalized areas of immature enamel crystallites (Figure 1-30). Using this basic outline in conjunction with clinical, histologic, and genetic criteria, Witkop and Sauk classified the various types of amelogenesis imperfecta (Box 1-1).

BOX 1-1**Witkop/Sauk Classification of Amelogenesis Imperfecta****HYPOPLASTIC**

Pitted, autosomal dominant
Local, autosomal dominant
Smooth, autosomal dominant
Rough, autosomal dominant
Rough, autosomal recessive
Smooth, X-linked dominant

HYPOCALCIFIED

Autosomal dominant
Autosomal recessive

HYPOMATURATION

Hypomaturation-hypoplastic with taurodontism, autosomal dominant
X-linked recessive
Pigmented, autosomal recessive
Snow-capped teeth

The following are clinical features useful for differentiating the three basic types of amelogenesis imperfecta:

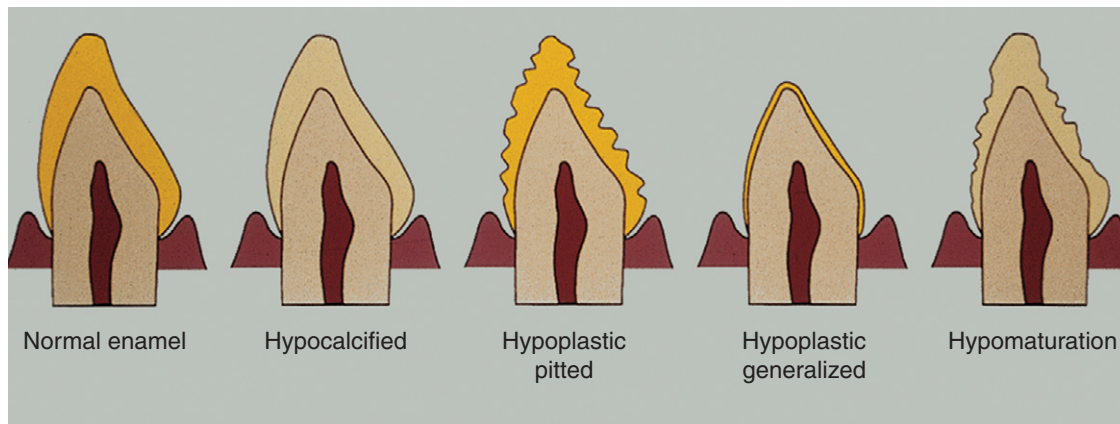
Hypoplastic type: The enamel is thinner than normal in focal (Figure 1-31) or generalized areas (Figure 1-32); the radiodensity of the enamel is greater than that of dentin.

Hypocalcified type: The enamel is of normal thickness but softer than normal and can be easily removed with a blunt instrument (Figure 1-33); the enamel is less radiodense than dentin.

Hypomaturation type: The enamel is of normal thickness but not of normal hardness and translucency (Figure 1-34, A); enamel can be pierced with the point of a dental explorer with firm pressure and can be chipped away from the underlying normal dentin; enamel radiodensity is about the same as dentin. The mildest form of the hypomaturation type exhibits enamel of normal hardness and has white opaque flecks in the incisal areas of the teeth (*snow-capped teeth*) (Figure 1-34, B).

CLINICAL FEATURES

The clinical appearance of the various types of amelogenesis imperfecta can be remarkably different. In some types the teeth appear essentially normal, whereas in others they may be extremely unsightly and obviously abnormal. Both dentitions are commonly affected to some degree. In the X-linked subtypes the clinical appearance differs between males and females.

**FIGURE 1-30**

Amelogenesis imperfecta. Enamel defects of basic types. Hypocalcified—normal thickness, smooth surface, less hardness. Hypoplastic, pitted—normal thickness, pitted surface, normal hardness. Hypoplastic, generalized—reduced thickness, smooth surface, normal hardness. Hypomaturation—normal thickness, chipped surface, less hardness, opaque white coloration.

**FIGURE 1-31**

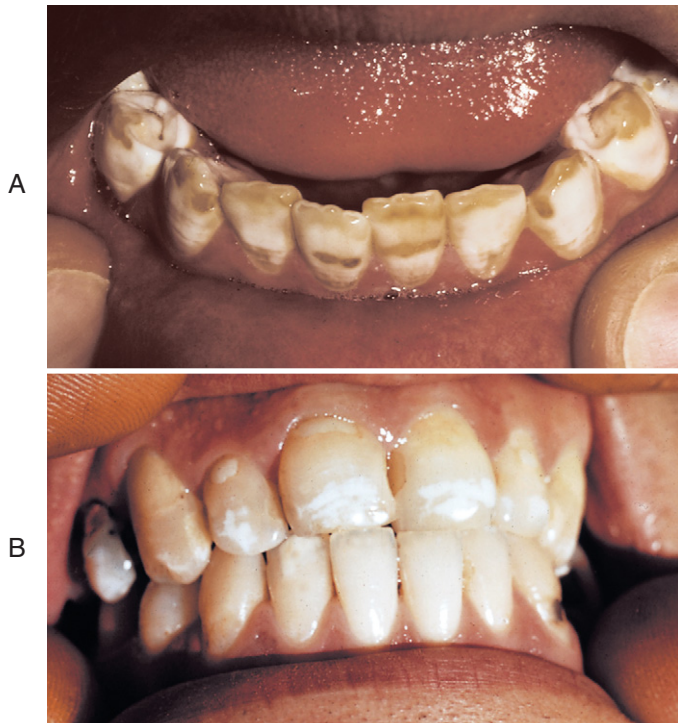
Focal hypoplastic amelogenesis imperfecta. The enamel is of normal thickness and hardness with diffuse pitting.

**FIGURE 1-32**

Generalized hypoplastic amelogenesis imperfecta. The enamel is evenly reduced in thickness but of normal hardness, resulting in spacing and alteration of the shape of teeth.

**FIGURE 1-33**

Hypocalcified amelogenesis imperfecta. The enamel is soft and easily chipped away, leaving exposed dentin that is easily stained, worn, and caries prone.

**FIGURE 1-34**

Hypomaturational amelogenesis imperfecta. **A**, Severe form with enamel of normal thickness but that exhibits loss of translucency and hardness, resulting in some chipping of incisal edges. **B**, In the mild form the teeth may be relatively normal but contain white flecks in the incisal third of the teeth (snow-capped teeth).

RADIOGRAPHIC FEATURES

The radiologic appearance of amelogenesis imperfecta varies with the type. In the smooth hypoplastic type, the enamel layer is conspicuously thin and its radiodensity is greater than the adjacent dentin; in the hypocalcified type, the enamel layer appears wispy or absent and is usually less radiodense than the adjacent dentin; in the hypomaturational type, the radiodensity of the enamel is almost equal to that of normal dentin.

DISTURBANCES IN STRUCTURE OF DENTIN

Local or systemic environmental factors that affect dentin formation also tend to affect enamel formation. Turner tooth and regional odontodysplasia are examples of disturbed dentin formation resulting from environmental factors. Generalized disturbances in dentin formation are usually hereditary and include conditions such as dentinogenesis imperfecta

(DI) and dentin dysplasia (DD). Familial hypophosphatemia (vitamin D-resistant rickets) is also in this category.

The two basic types of hereditary dentinal disturbances are (1) DI and (2) DD. DI is divided into three subtypes, and DD is divided into two subtypes. When grossly examined in a sagittal plane, the characteristic features of overall appearance and the shape of pulpal structures are useful in differentiating between the two types (Figure 1-35).

Dentinogenesis Imperfecta

DENTINOGENESIS IMPERFECTA: A hereditary defect consisting of opalescent teeth composed of irregularly formed and undermineralized dentin that obliterates the pulp chambers and pulp canals.

DI is an inherited disorder of dentin formation, usually exhibiting an autosomal dominant mode of transmission. This disorder has been classified into three types:

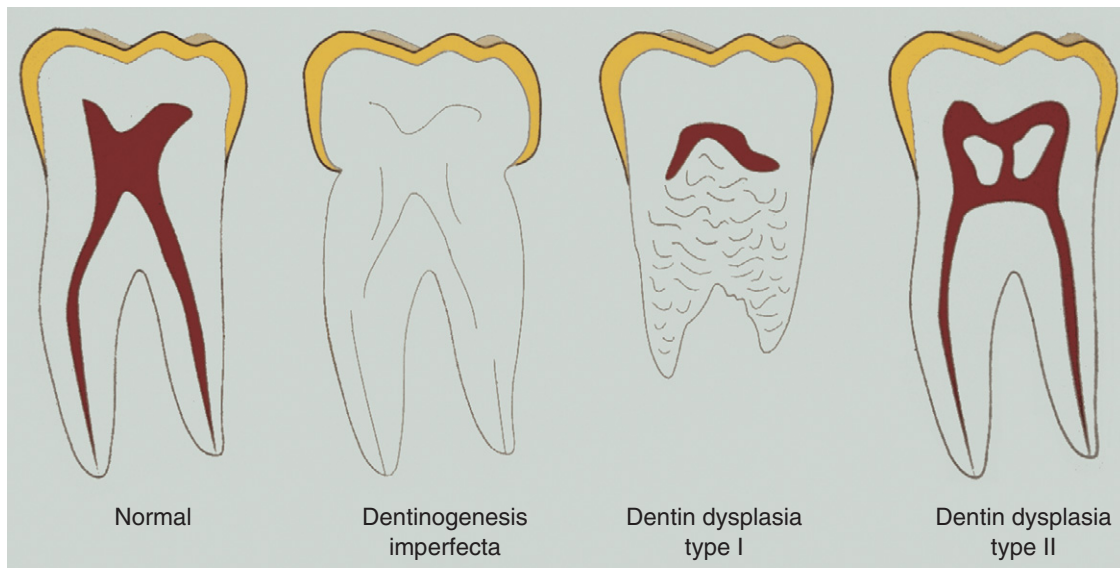
Type I: DI that occurs in patients afflicted with osteogenesis imperfecta (OI), although not all patients with OI exhibit DI. This type is usually inherited as an autosomal dominant trait. Although the teeth have the same opalescent color as in type II, patients often exhibit other features of OI such as having a bluish tint to the sclera of the eyes (Figure 1-36, A and B).

Type II: DI that is not associated with OI. The common term for this type of DI is *hereditary opalescent dentin*. It is the most common type and is inherited as an autosomal dominant trait. Incidence is approximately 1:8000 persons.

Type III: DI (Brandywine type) is rare and inherited as an autosomal dominant trait; it occurs in a racial isolate in the state of Maryland and has been considered as merely a homozygous expression of type II. Clinically, it is the same as type I and type II except that patients exhibit multiple pulpal exposures in the deciduous dentition.

CLINICAL FEATURES

In all three subtypes of DI, teeth of both dentitions are affected with variable clinical appearances. The teeth are opalescent with the color ranging from bluish-gray (Figure 1-37, A) to brown to yellowish. The dentin is abnormally soft, providing inadequate structural support to the overlying enamel. Although the enamel is normal, it fractures or chips away easily, exposing the occlusal and incisal dentin (Figure 1-37, B). The exposed soft dentin often undergoes rapid and severe functional attrition. Despite the exposure of dentin, teeth are not particularly prone to dental caries.

**FIGURE 1-35**

Hereditary disturbances of dentin. The characteristic morphologic features of the major types of dentin disturbances. Dentinogenesis imperfecta—constricted cemento-enamel junction and lack of pulpal structures. Dentin dysplasia, type I—normal crown, shortened roots, rippled dentin, chevron-shaped coronal pulp. Dentin dysplasia, type II—normal crown, normal length roots, pulpal chamber with large pulp stones.

**FIGURE 1-36**

Dentinogenesis imperfecta associated with osteogenesis imperfecta.

A, Patient's teeth exhibit characteristic opalescent coloration. **B,** Same patient with blue sclera of the eye.

RADIOGRAPHIC FEATURES

The teeth in DI subtypes I and II are similar and exhibit bulb-shaped crowns with constricted cemento-enamel junctions and thin roots (Figure 1-38, A). Depending on the age of the patient, the teeth will exhibit varying stages of obliteration of the pulp chambers and pulp canals (Figure 1-38, B). The cementum, periodontal ligament, and supporting alveolar bone appear normal. The teeth in DI type III may be similar to those seen in

types I and II, or they may exhibit extremely large pulpal chambers surrounded by a thin shell of dentin.

HISTOPATHOLOGY

The enamel in DI is normal. The mantle dentin, a narrow zone of dentin immediately beneath the enamel, remains nearly normal, whereas the remaining dentin is severely dysplastic (Figure 1-39, A). Within the dysplastic dentin are focal areas of an amorphous matrix

**FIGURE 1-37**

Dentinogenesis imperfecta (hereditary opalescent dentin). **A**, Patient's teeth with characteristic blue-gray (opalescent) appearance. **B**, Incisal edges reveal chipping of normal enamel, exposing soft dentin that undergoes rapid attrition.

FIGURE 1-38

Dentinogenesis imperfecta.

A, Radiograph of the teeth of a young patient that reveals the globe-shaped crowns caused by cervical constriction and obliteration of the coronal pulp.

B, Panoramic radiograph revealing the coronal shape and complete obliteration of the pulpal chambers of nearly all teeth.



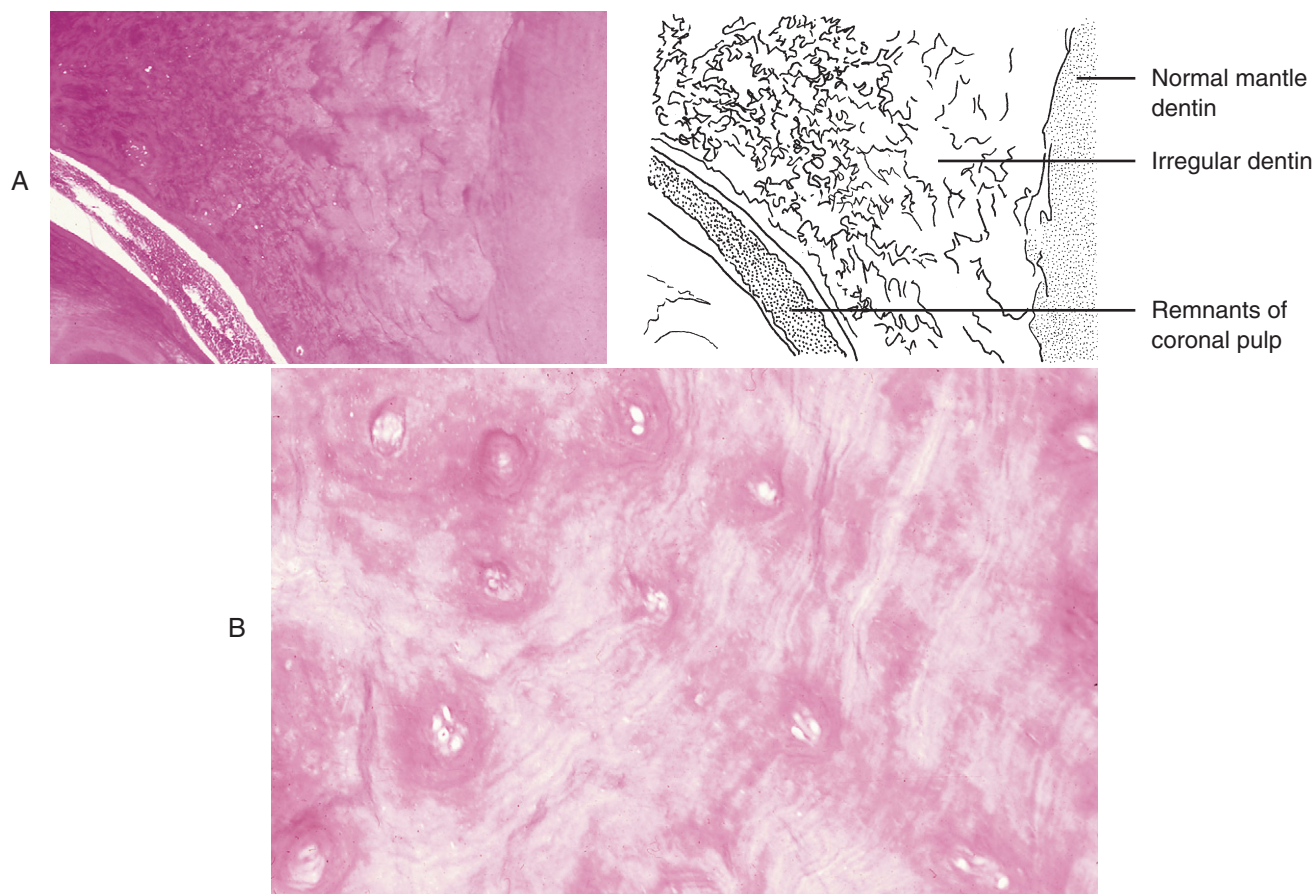


FIGURE 1-39

Dentinogenesis imperfecta. **A**, Low-power photomicrograph of dentin depicting the thin zone of normal mantle dentin on the right, with dysplastic irregular dentin replacing all but a small remnant of the coronal pulp. **B**, High-power photomicrograph demonstrating the large-sized and widely spaced dentin tubules and the lack of normal density of intertubular collagen deposits.

with globular and interglobular areas of mineralization. The dentinal tubules are disoriented, irregular, widely spaced, and usually larger than normal (Figure 1-39, *B*). Within the abnormal dentin, entrapped odontoblasts and degenerating cellular debris may be observed.

TREATMENT

The treatment of DI is directed toward preventing excessive loss of enamel and dentin through attrition and toward improving the teeth esthetically. This can be accomplished with appropriate restorations such as metal and porcelain composite crowns. Teeth affected by DI do not make good abutments for partial dentures, because root fractures may occur from the functional stress. In severe cases the need for complete dentures is almost inevitable.

Dentin Dysplasia

DENTIN DYSPLASIA: A hereditary defect in dentin formation in which the coronal dentin and tooth color are normal; the root dentin is abnormal with a gnarled pattern and associated shortened and tapered roots.

Dentin dysplasia (DD), originally termed “rootless teeth,” is an autosomal dominant inherited disorder characterized by abnormal dentin formation and abnormal pulpal morphology. The disorder has been classified into type I, radicular DD; and type II, coronal DD.

Type I (radicular DD): Although both types of DD are rare, type I is far more common than type II. All teeth in both dentitions are affected. The color of the teeth is usually within the normal range (Figure 1-40). In some cases the crowns of the teeth may exhibit a

**FIGURE 1-40**

Dentin dysplasia, type I. Patient exhibits normally shaped and colored teeth.

slight bluish or brownish translucency in the cervical region. The teeth usually exhibit a normal eruption pattern, although occasional delayed eruption has been reported. Affected teeth often exhibit increased mobility and may exfoliate prematurely.

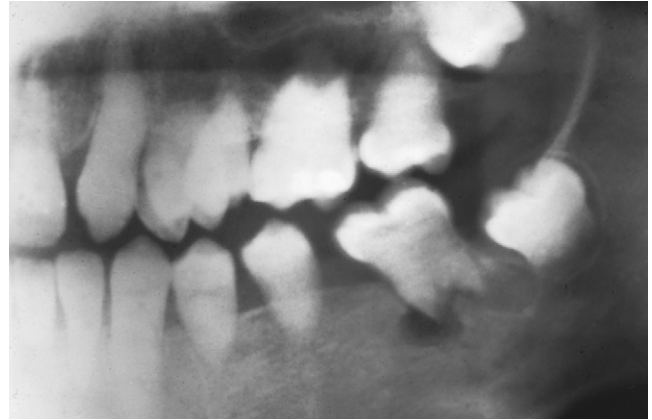
RADIOGRAPHIC FEATURES

The roots of the teeth are usually short, blunt, bulged, conic, or absent. The mandibular molars commonly have characteristic W-shaped roots. In the deciduous dentition, teeth often exhibit total obliteration of the pulpal chambers and canals. The permanent teeth may also exhibit pulpal obliteration; however, thin crescent-shaped or chevron-shaped remnants of the pulp chambers are often present. Periapical radiolucencies representing abscesses, granulomas, or cysts may be present in the absence of dental caries (Figure 1-41).

HISTOPATHOLOGY

The enamel and the mantle layer of dentin are normal. The remaining coronal and root dentin consist of a series of fused nodular masses composed of tubular dentin and osteodentin that have a histologic appearance which has been described as resembling lava flowing around boulders, gnarled burlwood, or a series of sand dunes (Figure 1-42, A). Occasionally, slitlike remnants of pulpal tissue may be seen between the normal and the abnormal nodular dentin masses. The junction between normal and abnormal dentin may be abrupt. The abnormal dentin is less dense and lacks regular distribution and orientation of tubular dentin (Figure 1-42, B).

Type II (coronal DD): Both the primary and permanent dentitions are affected in this type of DD; however, the clinical appearance of the deciduous teeth differs from that of the succeeding permanent teeth. Clinically the deciduous teeth exhibit a bluish-gray, brownish, or

**FIGURE 1-41**

Dentin dysplasia, type I. Panoramic radiograph depicting the obliteration of the pulp except for the occasional chevron radiolucency, shortened and W-shaped roots, and periapical radiolucency.

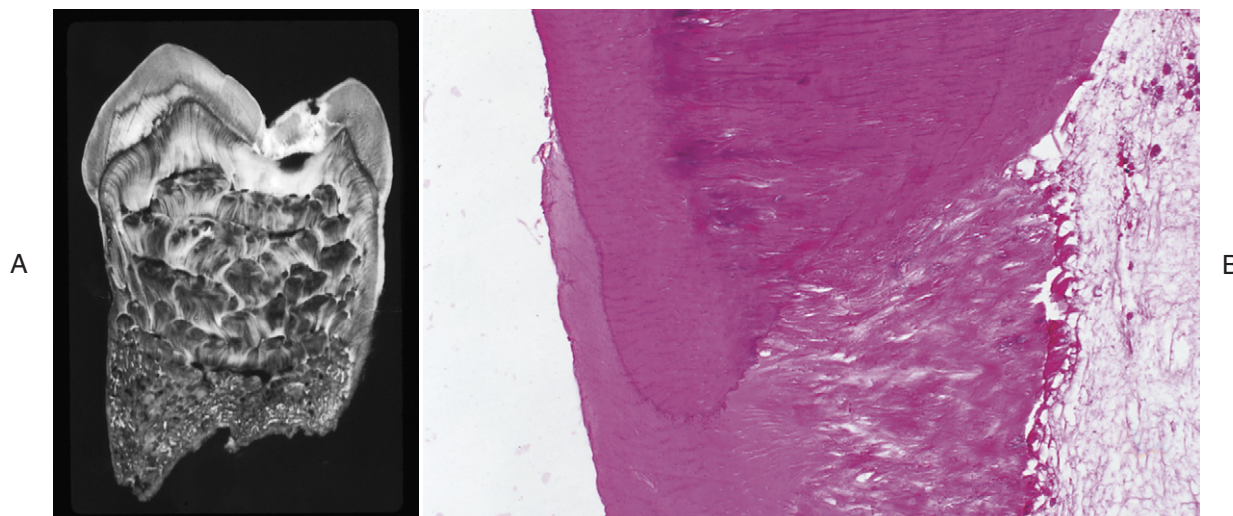
yellowish color and have the same translucent, opalescent appearance that is seen in DI. In contrast, the permanent teeth have a normal clinical appearance.

RADIOGRAPHIC FEATURES

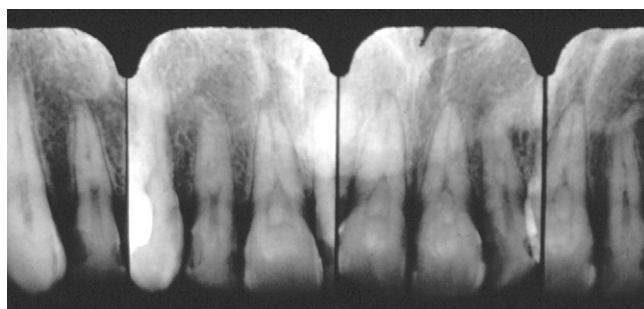
The deciduous teeth of DD type II exhibit obliterated pulpal chambers and canals that are similar to those seen in DD type I and in DI. The pulpal obliteration occurs after tooth eruption. The roots of the deciduous and permanent dentitions are of normal shape and length. The pulp chambers in the permanent teeth are abnormally large, rather than obliterated, and exhibit a radicular extension that imparts a thistle or flame shape to the root portion of the pulp. **Pulpal calcifications** (*pulp stones*) are visible in most of the coronal pulp chambers and the root pulp canals are narrowed (Figure 1-43).

HISTOPATHOLOGY

The deciduous teeth exhibit a normal zone of mantle dentin that changes abruptly into a dense amorphous mass of dentin exhibiting only occasional haphazardly arranged tubules. The permanent teeth exhibit a relatively normal coronal dentin except for the pulpal third, which exhibits areas of globular and interglobular dentin. The root dentin is amorphous and largely atubular. The pulp chamber exhibits numerous pulp stones; the pulp canals are narrow but otherwise normal. The prognosis for teeth in DD type I varies with the severity of the disorder. If the roots of the teeth are extremely short, early tooth loss is almost inevitable and appropriate prosthetic replacements will be required. If the roots are relatively normal, tooth loss may not be a major problem. The prognosis for the permanent teeth in DD type II is essentially the same as it is for normal teeth.

**FIGURE 1-42**

Dentin dysplasia, type I. **A**, Sectioned tooth revealing the gnarled and rippling formation of dysplastic dentin occupying the root portion of the tooth. **B**, Low-power photomicrograph of the junction of normal and dysplastic dentin revealing the abrupt transition and dysplastic nature of the root dentin.

**FIGURE 1-43**

Dentin dysplasia, type II. Periapical radiographs indicating teeth with relatively normal roots and pulp chambers that contain large pulp stones.

REGIONAL ODONTODYSPLASIA

REGIONAL ODONTODYSPLASIA: A developmental disturbance of several adjacent teeth in which the enamel and dentin are thin and irregular and fail to adequately mineralize; surrounding soft tissue is hyperplastic and contains focal accumulations of spherical calcifications and odontogenic rests.

Regional odontodysplasia (ROD), or *ghost teeth*, is a sporadically occurring nonhereditary disturbance of tooth development characterized by the defective for-

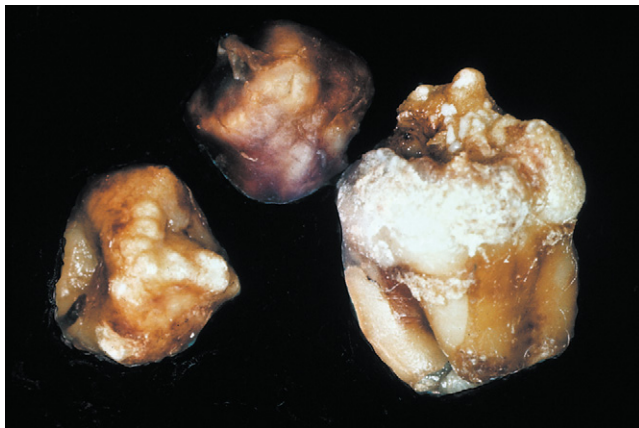
**FIGURE 1-44**

Regional odontodysplasia. Patient exhibiting a localized area of the mandible in which two abnormal teeth are present surrounded by an increase in the soft tissue.

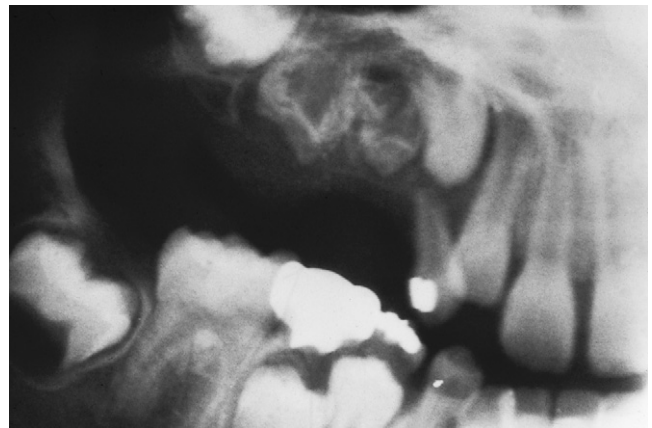
mation of enamel and dentin in addition to abnormal pulp and follicle calcifications. Although its cause is not fully understood, experimental evidence points to a local ischemic cause.

CLINICAL FEATURES

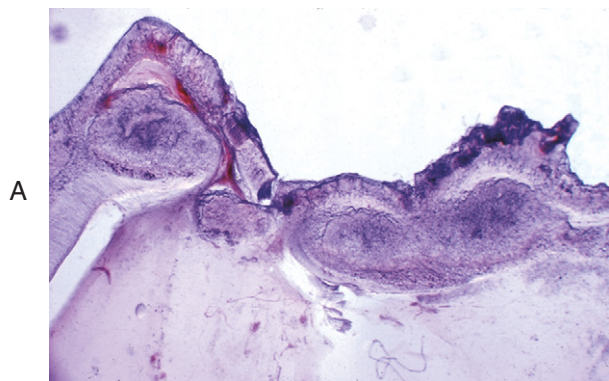
The disturbance more commonly appears in the maxilla than the mandible; it is *regional* in that it usually affects several contiguous teeth in a single quadrant (Figure 1-44). Involvement of two quadrants of the same arch has been reported. The condition is most commonly seen in the permanent dentition. The affected

**FIGURE 1-45**

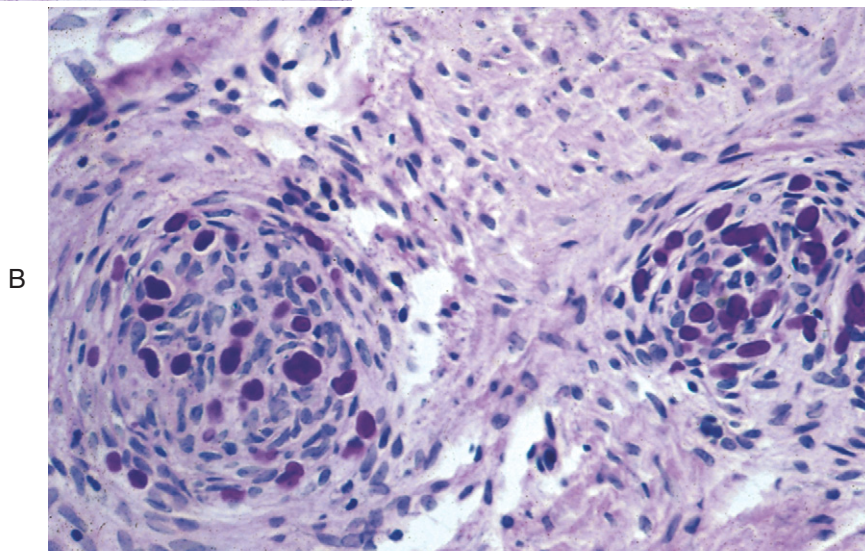
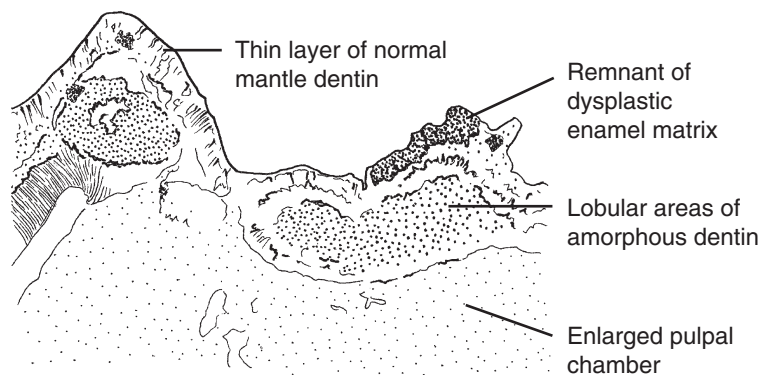
Regional odontodysplasia. Removed teeth reveal shortened roots and abnormally shaped crowns with a brown, leathery coloration and texture.

**FIGURE 1-46**

Regional odontodysplasia. Panoramic radiograph revealing several faint outlines of teeth in the posterior maxilla with large pulp chambers and lacking root formation.



A



B

FIGURE 1-47

Regional odontodysplasia. **A**, Low-power photomicrograph through the crown of a decalcified tooth depicting a remnant of the defective enamel matrix (thin normal mantle dentin overlying severely dysplastic dentin with lobular areas of amorphous dentin and a greatly enlarged coronal pulp chamber). **B**, Surrounding soft tissue contains nodular arrangements of connective tissue cells containing accumulations of spheric calcifications.

teeth exhibit a delay or a total failure to erupt. The teeth are considerably deformed with a soft leathery surface and are discolored, yellowish-brown (Figure 1-45).

RADIOGRAPHIC FEATURES

The teeth have been described as *ghost teeth* because of the marked decrease in radiodensity. The enamel and dentin are very thin and indistinct; the pulpal chambers are extremely large (Figure 1-46). Pulp stones may occasionally be visible.

HISTOPATHOLOGY

The dentin is dysplastic and characterized by irregular tubules, large areas of globular and interglobular dentin, and a widened predentin layer. The enlarged pulp chambers (Figure 1-47, A) exhibit numerous pulpal calcifications (pulp stones). The dental follicles are occasionally hyperplastic and exhibit significant numbers of epithelial odontogenic rests, numerous clusters of tiny droplet calcifications, and larger lamellar calcifications (Figure 1-47, B). Extraction of the affected teeth and replacement with a suitable prosthesis are usually required.

DISTURBANCES IN STRUCTURE OF CEMENTUM

Hypophosphatasia

Hypophosphatasia is inherited in the majority of cases as an autosomal recessive condition, but in some families it is inherited as an autosomal dominant with affected individuals having a milder clinical form. Hypophosphatasia is a disorder of bone mineralization caused by a deficiency in alkaline phosphatase in serum

and tissues. The cause of hypophosphatasia is a basic defect in the gene encoding for tissue nonspecific alkaline phosphatase (TNSALP). This gene has been mapped to the short arm of chromosome 1 (1p36-p34). The disorder is classified into neonatal, infantile, childhood, and adult forms. Hypophosphatasia is characterized by rachitic bone changes in infants and children and by osteomalacia in adults. Delayed formation and eruption of the dentition, premature loss of primary teeth, and the spontaneous loss of permanent teeth are characteristically seen in hypophosphatasia. The premature loss of deciduous teeth (especially the incisors) in the infantile form of the disorder appears to be related to the absence of dental cementum. Oral radiographs reveal that the teeth in these patients exhibit enlarged pulp chambers and pulp canals; however, the enamel is normal.

SOFT TISSUE CONGENITAL LIP PITS

Congenital lip pits are developmental defects that may involve the paramedial portion of the vermilion of the lower and upper lip (paramedial lip pit) or the labial commissure area (commissural lip pit) (Figure 1-48, A). Both types of lip pits appear to be inherited as an autosomal dominant trait. The paramedial lower lip pit may occur as an isolated finding or may be associated with cleft lip or cleft palate (Van der Woude syndrome). The gene for the majority of cases of this syndrome has been mapped to the long arm of chromosome 1 (1q32-q41). The paramedial lip pit may be unilateral or bilateral and occurs on the lower lip. Lip pits are congenital invaginations that can represent blind tracts (Figure 1-48, B) or dilated ectopic salivary ducts. Mucus secretion is visible

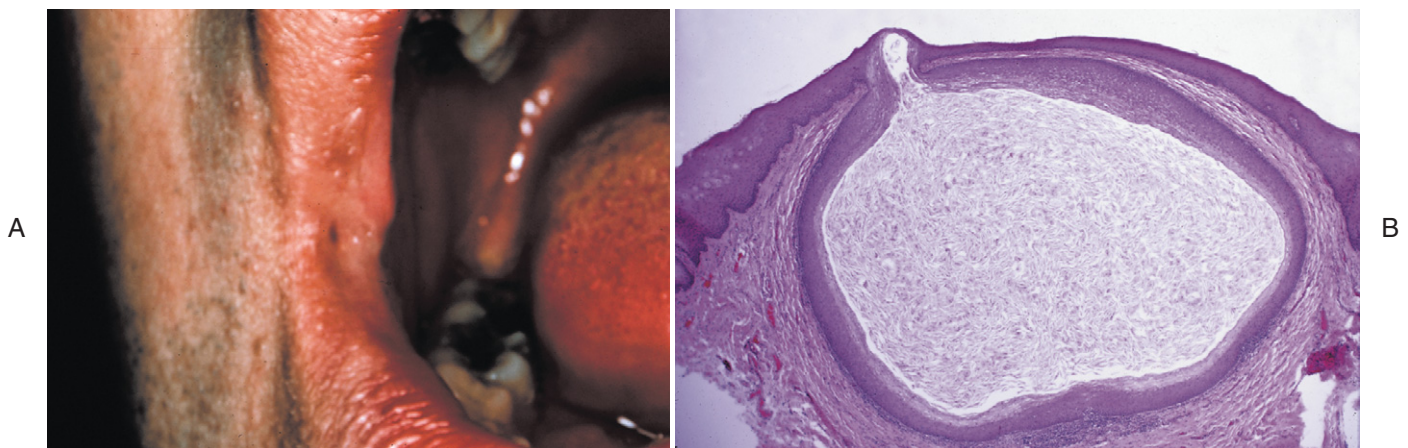


FIGURE 1-48

Congenital lip pit. **A**, An orifice of a lip pit is present in the angle (commissure) of the lips. **B**, Photomicrograph of removed lip pit that had become cystic. A layer of squamous epithelium lines the blind pouch, and the lumen is filled with desquamated epithelial cells.

at the opening of those pits that communicate with salivary gland tissue. The surface opening (pore) of the paramedial lip pit usually measures 1 to 3 mm in diameter; the depth will range from 5 to 15 mm. The commissural lip pit exhibits an opening of 1 to 2 mm and a depth of 2 to 4 mm. Although lip pits usually present no clinical problems, the paramedial lip pits are occasionally excised for cosmetic reasons; commissural lip pits require no treatment.

DOUBLE LIP

A double lip is an anomaly characterized by a horizontal fold of redundant mucosal tissue that is usually located on the inner aspect of the upper lip, although the lower lip can also be occasionally involved (Figure 1-49, A). This redundant tissue can be congenital or acquired. The double lip is usually visible when the lip is tense but not when the lip is at rest. Occasionally, the double lip will be seen in association with a fold of drooping skin above the upper eyelid (blepharochalasis) and with



FIGURE 1-49

A, Double lip phenomenon involving both upper and lower lips. **B**, Frenal tag involving the maxillary labial frenum in a teenage female.

nontoxic thyroid enlargement (Ascher syndrome). Although this redundant fold of tissue is occasionally excised for cosmetic reasons, double lip usually requires no treatment.

FRENAL TAG

The frenal tag is a redundant piece of mucosal tissue that projects from the maxillary labial frenum (Figure 1-49, B). Its shape and size varies from patient to patient. Although this tag of tissue has no known function, it is familial and appears to be inherited as an autosomal dominant trait. The frenal tag is often mistaken for an acquired fibrous hyperplasia caused by local injury or irritation and is therefore occasionally excised and submitted for pathologic examination. Histologically the frenal tag consists of normal oral mucosa.

ANKYLOGLOSSIA

ANKYLOGLOSSIA: *Lack of normal tongue mobility caused by the presence of an abnormal fibrous tissue attachment between its ventral surface and the floor of the mouth.*

Ankyloglossia, or *tongue-tie*, is a developmental anomaly characterized by an abnormally short and anteriorly positioned lingual frenum that results in severely restricted tongue movements and impaired speech. Occasionally, the abnormal lingual frenum connects the tip of the tongue to the anterior lingual gingiva (Figure 1-50), resulting in tension of the gingival tissue that progresses to local gingival and periodontal disease in the region of the frenal attachment. Ankyloglossia is best treated by surgically repositioning the lingual frenum.



FIGURE 1-50

Ankyloglossia. The tongue of the patient has reduced mobility caused by the large band of fibrous tissue extending from the ventral tongue to the lingual gingiva of the anterior mandible.

MACROGLOSSIA

Macroglossia, or *large tongue*, is a condition that may be congenital or secondary. Congenital macroglossia is seen in Down syndrome, Beckwith-Wiedemann syn-



FIGURE 1-51

Macroglossia. The tongue of the young patient is excessively large because of the presence of a lymphangioma.

drome, and occasionally in multiple endocrine neoplasia syndrome (type III). Secondary macroglossia can result from diffuse involvement of the tongue by tumors such as lymphangioma (Figure 1-51), hemangioma, or neurofibroma and from diffuse infiltration of the tongue by amyloid deposits in amyloidosis. Systemic conditions such as acromegaly (adult hyperpituitarism) and cretinism (congenital hypothyroidism) can also result in macroglossia.

FORDYCE GRANULES

Collections of sebaceous glands that occur in various locations within the oral cavity are termed *Fordyce granules*. Although they are most commonly seen bilaterally on the buccal mucosa and on the vermillion of the upper lip, they occur in various other intraoral sites, including the gingiva. Fordyce granules appear as multiple small, milia-like yellowish maculopapular structures that measure 1 to 2 mm in diameter (Figure 1-52, A). Because it is estimated that at least 80% of adults exhibit Fordyce granules to some extent, the presence of sebaceous glands in this area must be considered normal.

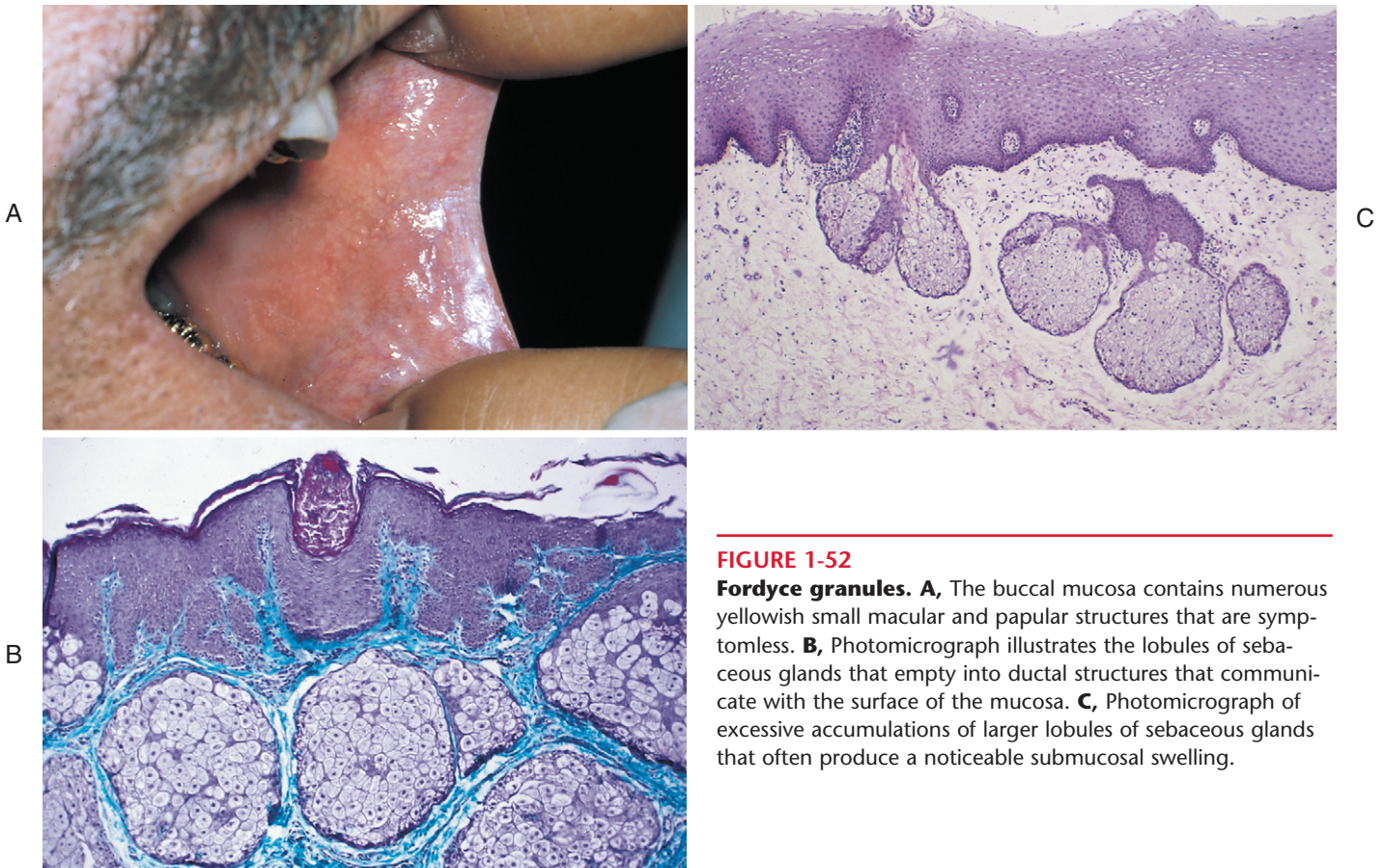


FIGURE 1-52

Fordyce granules. **A**, The buccal mucosa contains numerous yellowish small macular and papular structures that are symptomless. **B**, Photomicrograph illustrates the lobules of sebaceous glands that empty into ductal structures that communicate with the surface of the mucosa. **C**, Photomicrograph of excessive accumulations of larger lobules of sebaceous glands that often produce a noticeable submucosal swelling.

HISTOPATHOLOGY

Fordyce granules of the oral mucosa are identical to the normal sebaceous glands found in skin, except they are not associated with hair. The glands are usually superficial, composed of 1 to 5 lobules, and empty into a duct that opens on the mucosal surface (Figure 1-52, B). No treatment is required for this condition other than informing the patient of the nature of the entity.

Rarely a solitary sebaceous gland will undergo adenomatous hyperplasia and clinically present as a discrete, slightly elevated yellowish lesion measuring 5 to 10 mm in diameter. Histologically, these lesions are indistinguishable from Fordyce granules, except that they are larger, being composed of 15 or more sebaceous lobules (Figure 1-52, C). Most of these lesions appear to represent a localized focus of sebaceous hyperplasia rather than a sebaceous adenoma.

LEUKOEDEMA

LEUKOEDEMA: *Accumulation of fluid within the epithelial cells of the buccal mucosa.*

Leukoedema is an alteration of oral epithelium characterized by the intracellular accumulation of fluid (edema) within the spinous cell layer. The cause of this condition is presently unknown. It is so common in some racial groups that it is not considered to be a disease but a variation of normal.

CLINICAL FEATURES

Typically, leukoedema involves the buccal mucosa bilaterally, although the lateral borders of the tongue can also be affected. It is found in 85% to 95% of African Americans but only in 40% to 45% of whites. The affected mucosa exhibits an asymptomatic, diffuse, translucent, grayish-white, filmy appearance (Figure 1-53). In extreme cases the mucosa may be wrinkled or corrugated. When stretched, the appearance is greatly decreased. Mild degrees of leukoedema are common and often overlooked.

HISTOPATHOLOGY

Leukoedema is characterized by a mild degree of parakeratosis and acanthosis and a remarkable accumulation of intracytoplasmic fluid and glycogen, which results in enlarged spinous cells with clear cytoplasm and small, shrunken (pyknotic) nuclei. The associated underlying connective tissue is normal.

TREATMENT

Leukoedema is often included in the differential diagnosis of leukoplakias. Because of its bilateral nature, frequency of occurrence, and alteration in appearance when stretched, it is usually diagnosed clinically and does not require biopsy. No treatment is necessary.



FIGURE 1-53

Leukoedema. Buccal mucosa of the patient exhibits an asymptomatic white-gray superficial layer that does not rub off.

WHITE SPONGE NEVUS

WHITE SPONGE NEVUS: *An autosomal dominant hereditary condition in which the oral mucosa is white, thickened, and folded.*

White sponge nevus, also termed *white-folded gingivostomatitis*, *oral epithelial nevus*, and *Cannon disease*, is a relatively uncommon, autosomal dominant hereditary disorder that manifests as a white lesion of the oral mucosa. The cause of white sponge nevus is a mutation in the mucosal keratin pair K4 and K13. The associated genes have been mapped to the long arm of chromosomes 17 and 12 (17q21-q22, 12q13). The condition exhibits a variable penetrance; some patients exhibit lesions at birth, whereas in others, lesions may not appear until early childhood or even adolescence.

CLINICAL FEATURES

Lesions are asymptomatic, whitish, and often folded (corrugated). They may exhibit a translucent opalescence similar to that seen in leukoedema. Lesions may be widespread and involve various sites including the buccal mucosa (Figure 1-54, A), tongue (Figure 1-54, B), gingiva, palate, and floor of the mouth. In some patients, lesions may be present on other surfaces such as the mucosa of the anus and the nares.

HISTOPATHOLOGY

A mild-to-moderate hyperparakeratosis, acanthosis, and intracellular edema of the spinous layer characterize white sponge nevus. The nuclei of the spinous cells are shrunken (pyknotic). The associated connective tissue is usually free of inflammation. The diagnosis is generally

**FIGURE 1-54**

White sponge nevus. Patient with asymptomatic white folded superficial layer of the buccal mucosa (**A**) and tongue (**B**) that has been present for most of the patient's life.

reached by combining its histopathologic features, clinical appearance, and the patient's family history.

TREATMENT

The condition requires no treatment, because it is entirely benign. The patient often benefits from an explanation of the nature of the condition and its hereditary pattern so that future clinicians who observe the condition during routine examinations do not advise additional diagnostic procedures.

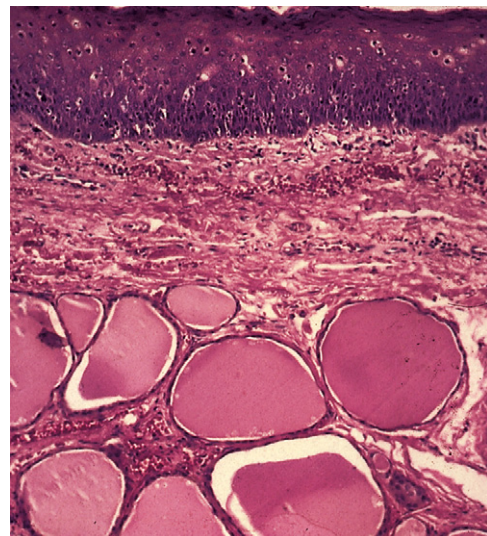
LINGUAL THYROID NODULE

LINGUAL THYROID NODULE: A submucosal nodule of accessory thyroid tissue located in the midposterior tongue.

A lingual thyroid nodule is a rare anomaly characterized by the development of a submucosal mass of thyroid tissue on the midposterior dorsum of the tongue. Embryologically, the thyroid gland anlage arises at the site of the foramen caecum and migrates inferiorly along the thyroglossal tract to its ultimate destination in the anterior neck. If all or part of the thyroid anlage fails to migrate, remnants of thyroid tissue can develop along its path of migration; a lingual thyroid nodule represents a thyroid remnant in the region of the thyroid gland's origin. Microscopic examination of human tongues removed at autopsy reveals that despite the absence of a clinically apparent thyroid nodule, as many as 10% exhibit remnants of thyroid tissue within the tongue.

CLINICAL FEATURES

A lingual thyroid nodule is far more common in females and most commonly becomes clinically apparent during puberty and adolescence. It presents as a 2 to 3 cm smooth sessile mass located on the midposterior

**FIGURE 1-55**

Normal thyroid tissue in a lingual thyroid nodule of the posterior tongue.

dorsum of the tongue, in the region of the foramen caecum. The chief symptoms are dysphagia, dysphonia, dyspnea, and a feeling of tightness in the area.

HISTOPATHOLOGY

Most cases are composed of normal mature thyroid tissue (Figure 1-55), although embryonic or fetal thyroid tissue may also be seen.

TREATMENT

Before excision of a lingual thyroid nodule is planned, it should be determined if the patient possesses a functioning thyroid gland in the anterior neck with sufficient

secretion to support the daily requirement when the supplementary source in the tongue is removed. If a normal thyroid gland is present, then the lingual nodules can be excised. If a subnormal thyroid gland has developed in the anterior neck as a result of the ancillary source, then thyroid replacement therapy may be required.

ORAL TONSIL

Tonsillar lymphoid tissue is primarily distributed in a circular arrangement (Waldeyer ring) in the posterior region of the mouth. It consists of three main masses of lymphoid tissue, namely the paired palatine (faucial) tonsils, the pharyngeal tonsils (adenoids), and the lingual tonsil located at the base of the tongue. The lingual tonsil often extends anteriorly along the posterolateral borders of the tongue and includes the region of the foliate papillae. Reactive lymphoid hyperplasia of the lingual tonsil in this location is sometimes termed *foliate papillitis*. In children and adolescents, tonsillar tissue may also be visible as discrete, slightly elevated reddish papules in the floor of the mouth on either side of the lingual frenum (Figure 1-56). These islands of extrapharyngeal tonsillar tissue are termed *oral tonsils*. Oral tonsils consist of lymphoid aggregates that exhibit germinal centers surfaced by nonkeratinized squamous epithelium, with or without occasional crypts. Oral lymphoepithelial cysts occasionally develop at the site of oral tonsils in the floor of the mouth or the lingual tonsils on the posterior lateral border of the tongue.

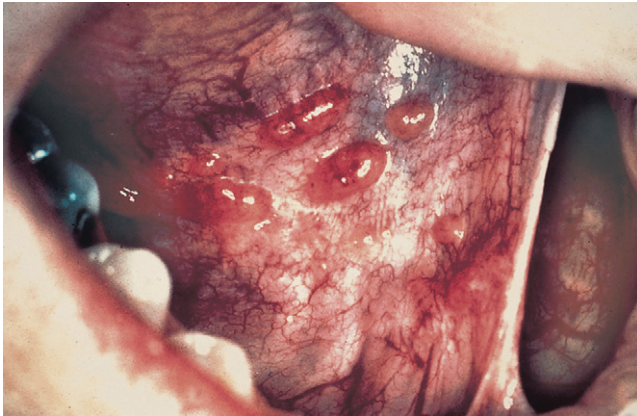


FIGURE 1-56

Oral tonsil presenting as slightly raised mucosal plaques on the anterior floor of the mouth.

RETROCUSPID PAPILLA

The retrocuspid papilla is a 2 to 4 mm slightly raised area of mandibular alveolar mucosa located lingual to the cuspids, between the marginal gingiva and the

mucogingival junction. It is commonly bilateral but can also be unilateral, and it is more prominent in children. Because retrocuspid papilla is commonly bilateral and has a very specific location, it is logical to assume that it represents a normal anatomic structure. Histologically, a retrocuspid papilla exhibits a striking resemblance to an incisive papilla; it is often composed of highly vascular fibrous connective tissue surfaced by orthokeratinized or parakeratinized squamous epithelium. Gross anatomic examination of human mandibles suggests that the retrocuspid papilla is analogous to an incisive papilla, representing a focus of fibrovascular tissue covering the osseous foramen of a nutrient blood vessel.

BONE HEMIFACIAL HYPERTROPHY

Although most humans exhibit some degree of facial asymmetry, only individuals who exhibit significant unilateral enlargement of the face are considered to exhibit *hemifacial hypertrophy*. Although a number of factors have been proposed to explain this condition, the most plausible appears to be an increased neurovascular supply to the affected side of the face. Either side of the face can be affected, and a slight female predilection exists. Unilateral enlargement of the facial soft tissue, bones, and teeth is usually present. Specifically, the asymmetry usually involves the frontal bone, maxilla, palate, mandible, alveolar process, condyles, and associated soft tissue (Figure 1-57, A). On the affected side, the skin is thick and coarse, the hair is thick and abundant (hypertrichosis), and the sebaceous and sweat gland secretions are excessive. The ear and eye on the affected side may also be enlarged. Unilateral enlargement of the cerebral hemispheres may be responsible for the mental retardation seen in 15% to 20% of these patients and for the occurrence of seizures. Intraorally, a unilateral macroglossia (Figure 1-57, B) with an increase in the size of the fungiform papillae is often present. The roots and crowns of the teeth, particularly the permanent teeth, are often enlarged and may erupt prematurely. Because of the osseous and dental asymmetries, malocclusion is common (Figure 1-57, C). Patients with hemifacial hypertrophy may exhibit an increased incidence of certain visceral tumors, particularly Wilms' tumor of the kidney. On rare occasions the hypertrophy may extend beyond the face and include the entire side of the body.

The differential diagnosis of hemifacial hypertrophy should include neurofibromatosis, fibrous dysplasia, and arteriovenous malformation of the jaws. No specific treatment exists for hemifacial hypertrophy, although selective surgical treatment to improve functional and cosmetic abnormalities may be required in some cases.



FIGURE 1-57

Hemifacial hypertrophy. The patient exhibits extensive disproportionate growth of the whole left side of the cranium, midface, and mandible (**A**); the left side of the tongue (**B**); and a severe malocclusion (**C**).

HEMIFACIAL ATROPHY

Hemifacial atrophy, also known as **Romberg syndrome**, is a rare condition characterized by a progressive decrease in the size of one side of the face. Occasionally, other parts of the body may also be affected. Although the cause of the condition is presently unknown, peripheral nerve dysfunction, trauma, infection, heredity, and a regional unilateral progressive systemic sclerosis have been proposed as possible causes.

Clinically, the condition usually begins in the first or second decade of the patient's life. The tissues of the face, including the skin, subcutaneous tissue, muscle, and bone, are affected to varying degrees. The affected side of the face may become hyperpigmented, and a slightly depressed vertical furrow may become apparent at the midline of the forehead and brow. As the condition progresses, a hollowing of the cheek and the orbit may appear on the affected side. The left side of the face is more commonly affected than the right side. Other features that may accompany hemifacial atrophy include trigeminal neuralgia, ocular changes, facial hair loss, and contralateral jacksonian epilepsy. Intraorally, a unilateral atrophy of the lips and tongue are often present. The jawbones and the roots of teeth on the affected side may exhibit delayed development, and tooth eruption may be retarded. No known treatment for hemifacial atrophy exists; however, progression of the condition usually ceases after a few years and remains static for the remainder of the patient's life.

CLEFT LIP AND CLEFT PALATE

CLEFT LIP: A developmental defect, usually of the upper lip, characterized by a wedge-shaped defect resulting from the failure of two parts of the lip to fuse into a single structure.

CLEFT PALATE: A developmental defect, usually of the upper lip, characterized by a wedge-shaped defect resulting from the failure of two parts of the lip to fuse into a single structure.

Because cleft lip and cleft palate are developmentally related and often occur together, they are discussed together. The cause of cleft lip and cleft palate appears to involve both hereditary and environmental factors. Research indicates that approximately 40% of cleft lip cases, with or without cleft palate, appear to be hereditary, whereas less than 20% of isolated cleft palate cases appear to be hereditary. This type of genetic data suggests that cleft lip, with or without cleft palate, is distinct from isolated cleft palate.

A number of different studies have shown that most cleft cases are polygenic (influenced by several different genes acting together). In this context it is presumed that every individual carries some genetic liability for

clefing, and only if the combined liabilities of the parents exceed a minimum threshold does clefing occur in their offspring. Clefing occurs in numerous syndromes, which collectively represent approximately 5% of all cleft cases. In these syndromes, however, the clefing appears to be monogenic (influenced by a single gene) rather than polygenic. Although it is generally agreed that heredity is probably the most important single factor in cleft lip and cleft palate, a number of environmental factors have also been investigated.

Six environmental factors that have been postulated to play an accessory role in the development of cleft lip and cleft palate include (1) nutritional factors such as deficiency of or excess of vitamin A and riboflavin deficiency; (2) physiologic, emotional, or traumatic stress; (3) relative ischemia to the area; (4) mechanical obstruction by an enlarged tongue; (5) substances such as alcohol, drugs, or toxins; and (6) infections. Experimental animal studies using vitamin A deficiency, vitamin A excess, riboflavin deficiency in pregnant rats, and cortisone administration in pregnant rabbits have resulted in an increased incidence of cleft palate; no similar effects have been proven to occur in

humans. Stress-induced hydrocortisone secretion in humans, analogous to cortisone administration in rabbits, has been postulated, but not conclusively proven, to result in cleft palate formation.

CLINICAL FEATURES

Clefts of the lip and palate can be classified into four major categories: (1) cleft lip, (2) cleft palate, (3) unilateral cleft lip and palate, and (4) bilateral clefts of the lip and palate (Figure 1-58, A-C). Clefts of the upper lip can be classified as follows: (1) unilateral incomplete, (2) unilateral complete, (3) bilateral incomplete, and (4) bilateral complete.

Cleft deformities of the oral regions are extremely variable in complexity (Figure 1-59, A). They range from a minimal deformity such as a bifid uvula (Figure 1-59, B) or a mild notch of the upper lip to severe bilateral clefts that involve the lip, alveolus, and the entire hard and soft palate (Figure 1-59, C). Cleft palate usually results in a direct communication between the oral and nasal cavities, resulting in significant functional impairment. Approximately 50% of isolated cleft palates are associated with other developmental abnormalities such as

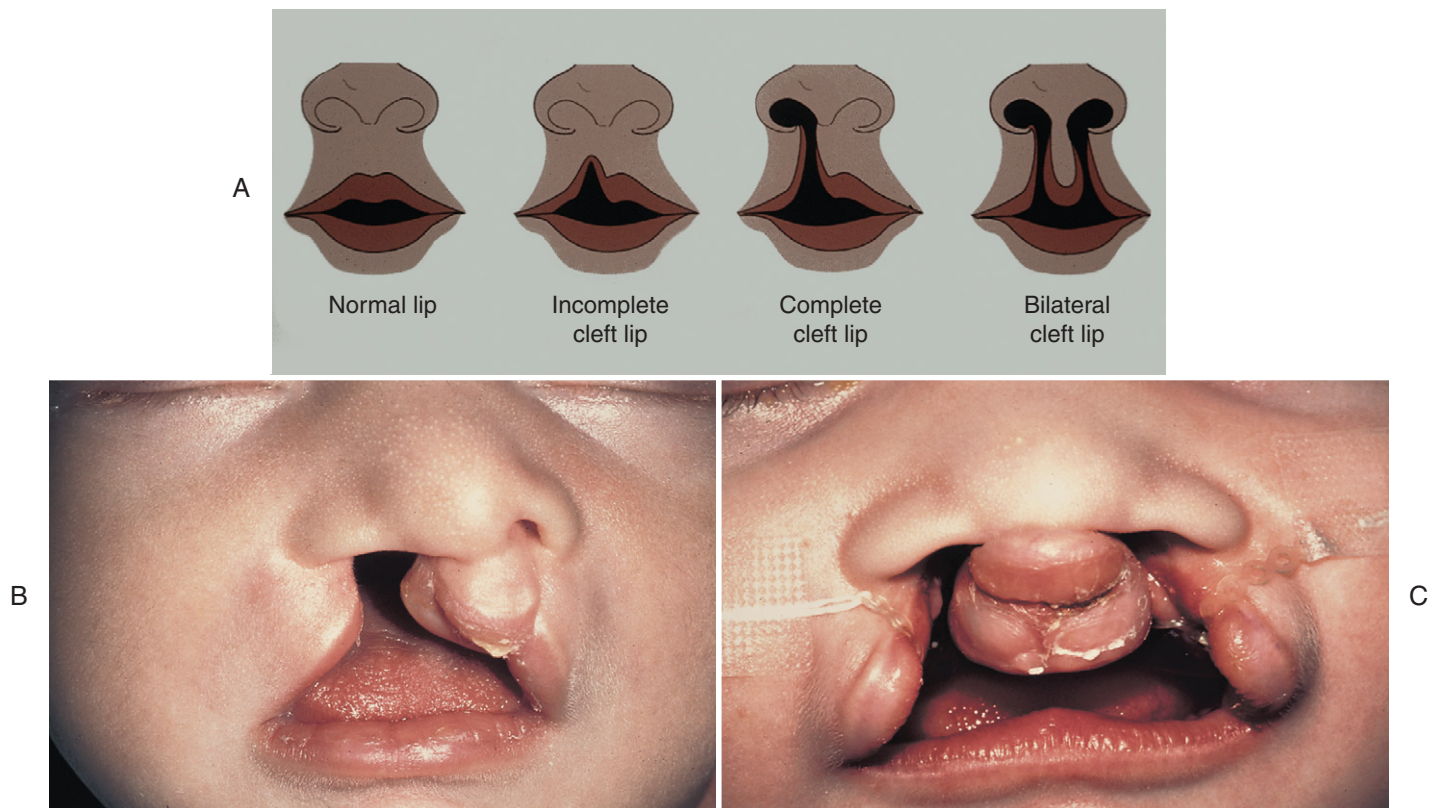


FIGURE 1-58

Cleft lip. **A,** The common presentations of congenital defects in lip formation.

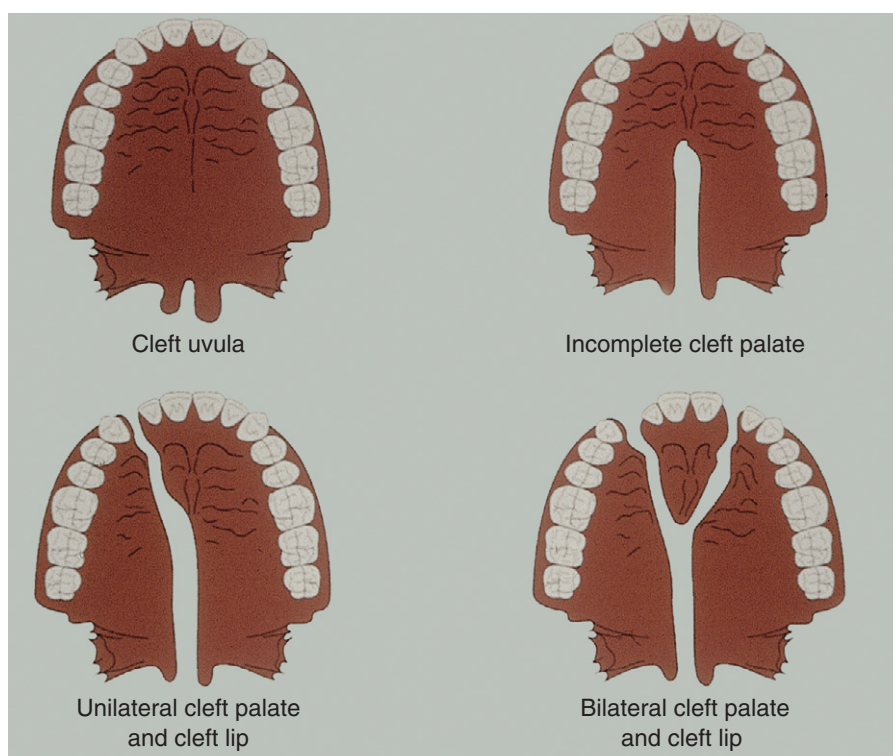
B, Unilateral cleft lip and palate. **C,** Bilateral cleft lip and palate. (Courtesy Dr. Ralph A. Latham.)

congenital heart disease, polydactyly and syndactyly, hydrocephalus, microcephalus, clubfoot, supernumerary ear, hypospadias, spina bifida, hypertelorism, and mental deficiency.

The incidence of the different types of clefts varies significantly. For example, clefts of the upper lip are relatively common, whereas clefts of the lower lip are extremely rare. Unilateral cleft upper lip accounts for approximately 80% of all cleft lips. The combined cleft lip and cleft palate is the most common type of cleft deformity, accounting for approximately 50% of all cleft cases. Cleft lip and cleft palate are somewhat more common in males than in females, whereas isolated cleft palate is more common in females. The incidence of

cleft lip and cleft palate ranges between 1:700 and 1:1000 births. Isolated cleft lip and cleft palate each account for approximately 25% of the cases. The incidence of isolated cleft palate ranges between 1:1500 to 1:3000 births.

The median maxillary anterior alveolar cleft that occurs in approximately 1% of the population is unrelated to the cleft lip or cleft palate. In this particular type of cleft, the defect is limited to bone and no breach exists in the continuity of the soft tissue. The cleft can be visualized radiographically as an incomplete closure of the median fissure of the anterior maxilla. Clinically, a wide diastema is often present between the maxillary central incisors.



A



B

C

D

FIGURE 1-59

Cleft lip and palate. **A**, The common presentations of congenital defects in palate formation. **B**, Bifid uvula. **C**, Unilateral cleft lip and palate, before treatment. **D**, Unilateral cleft lip and palate, after treatment. Same patient as shown in **C**. (**B**, Courtesy Dr. Tom Daley; **C** and **D**, Courtesy Dr. Ralph A. Latham.)

TREATMENT

Cleft lip is usually treated surgically during the first month of a patient's life. In most cases surgical repair achieves excellent cosmetic and functional results (Figure 1-59, D). Before treatment, cleft palate usually causes significant eating and drinking problems for the patient, with regurgitation of food and drink through the nose being particularly problematic. Surgical treatment of cleft palate is usually delayed until the patient is approximately 18 months of age. By this time significant growth has occurred, but speech habits have not yet been established. Surgical closure of cleft palate can be achieved in most cases; however, varying amounts of speech training may be required to overcome any functional deficiency. Therapeutic support may be needed to overcome any psychologic trauma that the patient may have experienced before treatment.

LINGUAL MANDIBULAR SALIVARY GLAND DEPRESSION

LINGUAL MANDIBULAR SALIVARY GLAND

DEPRESSION: A developmental concavity of the lingual cortex of the mandible, usually in the third molar area, that forms around an accessory lateral lobe of the submandibular gland and has the radiographic appearance of a well-circumscribed cystic lesion within the bone, usually below the inferior alveolar canal.

The lingual mandibular salivary gland depression is also known as *Stafne cyst*, *static bone cyst*, and *latent bone cyst*. It is a relatively uncommon entity that presents as a distinct, localized, deep concavity (depression) located on the lingual aspect of the mandible, between the mandibular canal and the inferior border of the mandible (Figure 1-60, A). Although most commonly seen in the molar region, this entity can occasionally involve the lingual aspect of the anterior mandible. Most reported cases of this entity have been in males. Sialography has shown that an accessory lateral lobe of the submandibular salivary gland usually occupies the concavities in the molar region. Surgical exploration and biopsy of the contents of these concavities generally reveals normal submandibular salivary gland tissue (Figure 1-60, B). Although the radiologic appearance and the anatomic location of this entity are considered to be characteristic, sialography or magnetic resonance imaging (MRI) can be used to confirm the salivary gland nature of this entity. No treatment is required.

FOCAL OSTEOPOROTIC BONE MARROW DEFECT

The focal osteoporotic bone marrow defect is an ill-defined radiolucency found in an edentulous area of the mandible that was previously occupied by a tooth. The

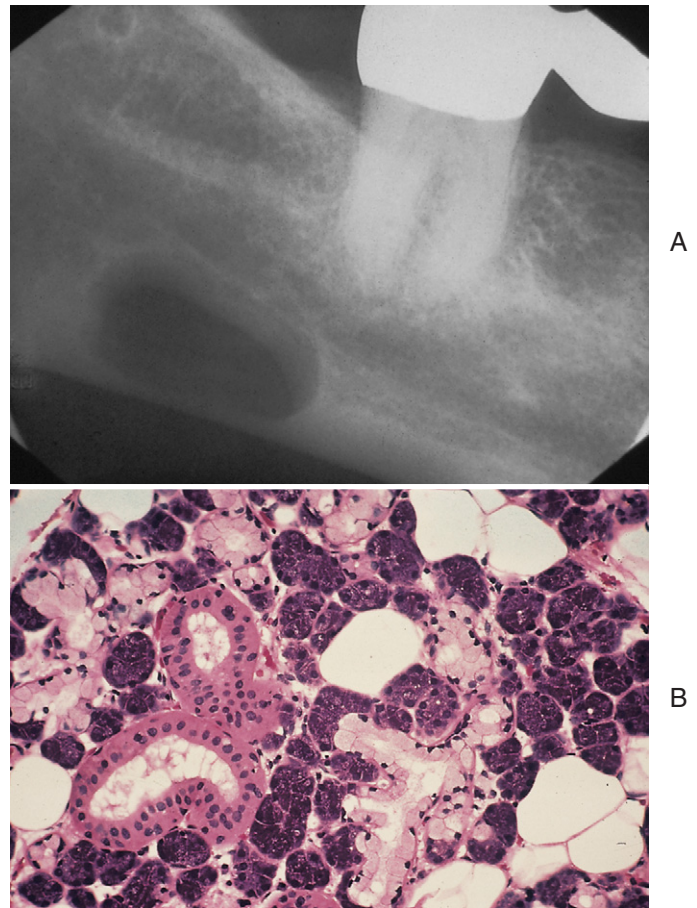


FIGURE 1-60

Lingual mandibular salivary gland depression. **A**, Radiograph of molar area of mandible revealing the presence of an oval-shaped, circumscribed radiolucency beneath the inferior alveolar canal that is not in continuity with the apices of the overlying molar. **B**, Histologically normal submandibular salivary gland tissue removed from a submandibular salivary gland depression. (**A**, Courtesy Dr. Heddie O. Sedano.)

most commonly proposed theory of pathogenesis is that after an extraction, the defect is replaced with hematopoietic marrow rather than the trabecular bone normal for the area.

The defect is symptomless, and no cortical expansion is found during a routine radiographic survey. It is found predominantly in middle-age females (in the mandibular molar area). The radiographic appearance is variable, ranging from a rounded, barely noticeable mixed radiolucent-opaque lesion to a diffuse, irregularly shaped radiolucent area with faint wisps of a trabecular pattern (Figure 1-61, A and B). The microscopic appearance consists of normal hematopoietic elements with the usual spectrum of blast and mature cells in the erythrocytic, myelocytic, lymphocytic, and megakaryocytic series (Figure 1-61, C). This

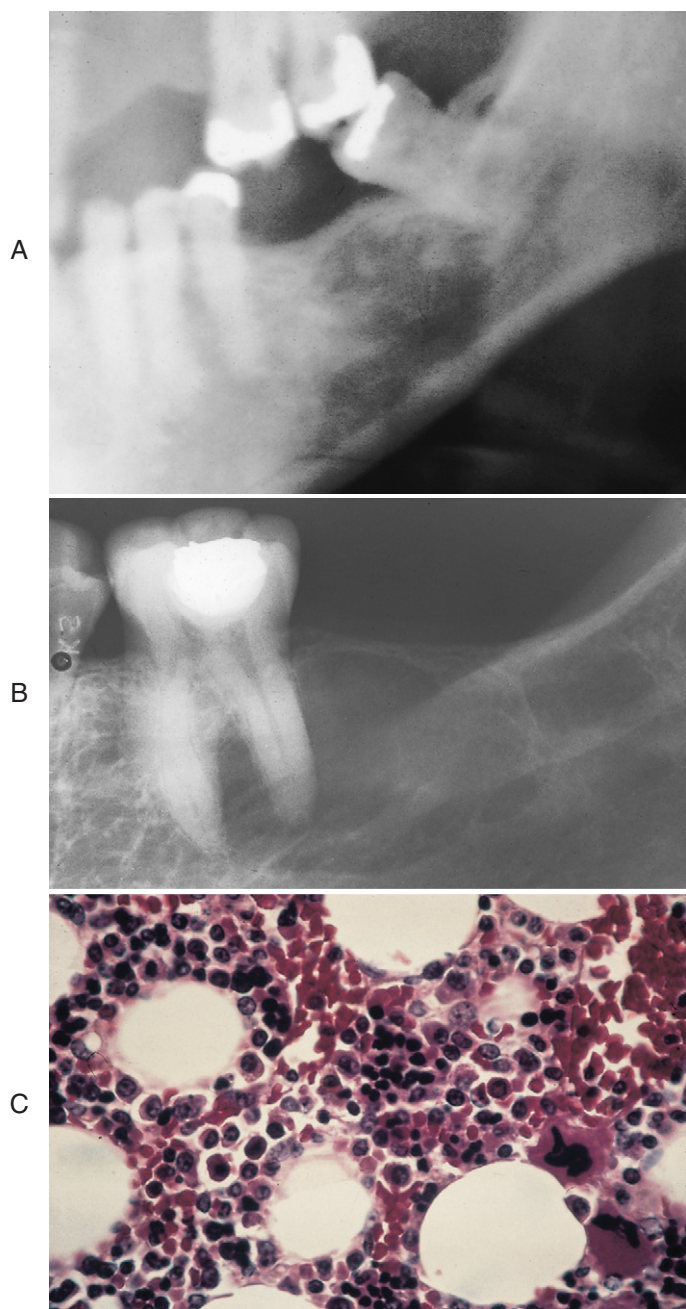


FIGURE 1-61

Focal osteoporotic bone marrow defect. **A**, Radiographs of edentulous areas of the posterior mandible containing an asymptomatic irregularly shaped mixed radiolucent/radiopaque lesion. **B**, A unilocular, mostly radiolucent area with faint wisps of bone. **C**, Histologically normal bone marrow removed from an osteoporotic bone marrow defect.

is in contrast to the adipose marrow commonly found in this location.

Because the radiographic appearance is nearly indistinguishable from more serious conditions such as

Langerhans cell histiocytosis, metastatic carcinoma, and multiple myeloma, incisional biopsy is usually necessary. Once the diagnosis is confirmed, no further treatment is necessary.

CLEIDOCRANIAL DYSPLASIA

Cleidocranial dysplasia is a syndrome in which the patient experiences abnormal growth of the bones of the face, skull, and clavicles, with a concomitant tendency for failure of tooth eruption. The syndrome may be hereditary with an autosomal dominant pattern or appear as a spontaneous mutation. The degree of involvement varies widely. The gene responsible for cleidocranial dysplasia has been mapped to the short arm of chromosome 6 (6p21).

CLINICAL FEATURES

The striking features in the appearance of the patients with high expressivity are the disproportionate growth of the facial and skull bones (producing the characteristic facial appearance) and their ability to appose the shoulders to near the midline of the chest. The frontal and occipital skull plates are enlarged (bossing), whereas the other bones may remain relatively normal, producing an enlarged and abnormally shaped head (Figure 1-62, A).

RADIOGRAPHIC FEATURES

Radiographs of these bones usually reveal tortuous suture lines (wormian bones) and some areas in which the sutures are greatly widened caused by the lack of sufficient bone growth within the plates (Figure 1-62, B). This is in contrast to an underdeveloped midface and a maxilla that appears depressed, particularly in relation to the enlarged forehead. The nose is commonly flat, wide, and lacks a bridge. Although the mandible may be of normal size, it appears enlarged because of the hypoplastic maxilla. The clavicles may be bilaterally absent or may be partially present, exhibiting varying degrees of hypoplasia (Figure 1-62, C).

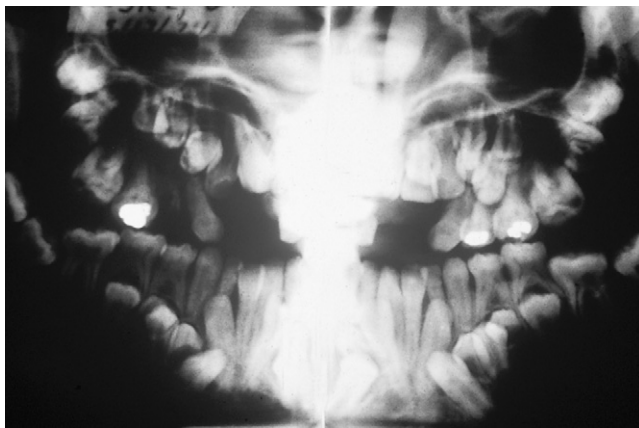
Intraorally, patients may retain the primary dentition into adulthood; radiographs reveal numerous fully formed teeth embedded within the mandible and maxilla, many of which are supernumerary (Figure 1-63). The palate is usually highly arched and narrow.

TREATMENT

No known treatment exists for patients with cleidocranial dysplasia, except counseling regarding its mode of inheritance. Extraction of primary teeth does not necessarily result in eruption of the secondary dentition, although exposure combined with orthodontic procedures may be helpful in some cases.

**FIGURE 1-62**

Cleidocranial dysplasia. **A**, Typical facies of patient exhibiting bossing of frontal bones, depressed midface, and prominent chin. **B**, Lateral cranial radiograph depicting the disproportionately large frontal and occipital bones, tortuous suture lines (wormian bones), and depressed midfacial bones. **C**, The patient is able to approximate the shoulders as a result of aplasia or extensive hypoplasia of the both clavicle bones. (Courtesy Dr. Richard K. Wesley.)

**FIGURE 1-63**

Cleidocranial dysplasia. Panoramic radiograph of dentition demonstrating the presence of a permanent dentition with associated supernumerary teeth embedded within the mandible and maxilla and deciduous dentition that has failed to exfoliate.

CROUZON SYNDROME (CRANIOFACIAL DYSOSTOSIS)

Crouzon syndrome (craniofacial dysostosis) is an uncommon, autosomal dominant craniofacial disorder characterized by the premature closure of cranial bone sutures (craniosynostosis). This syndrome is due to a mutation in the fibroblast growth factor 2 (FGF2). It occurs in about 1 of every 25,000 births. Although this syndrome exhibits variable expressivity, the predominant clinical features include maxillary hypoplasia, short upper lip, widely spaced eyes (hypertelorism), shallow orbits, protruding eyeballs (ocular proptosis), short head (brachycephaly), and calcified stylohyoid ligaments (Figure 1-64). Because of maxillary hypoplasia, the dental arch width is reduced; crowding of the maxillary teeth is common. Two-thirds of Crouzon patients exhibit a unilateral or bilateral posterior crossbite. Radiographs of the skull typically exhibit increased

**FIGURE 1-64**

Crouzon syndrome (craniofacial dysostosis). Facies exhibiting maxillary hypoplasia, short upper lip, widely spaced eyes (hypertelorism), and protruding eye (ocular proptosis). (Courtesy Dr. Heddie O. Sedano.)

digital markings (*beaten metal pattern*). Approximately 50% of these patients exhibit poor vision and hearing deficits. Some of the developmental defects in this syndrome can be corrected surgically.

TREACHER COLLINS SYNDROME (MANDIBULOFACIAL DYSOSTOSIS)

Treacher Collins syndrome (mandibulofacial dysostosis) is an autosomal dominant disorder characterized by the abnormal development of structures derived from the first and second branchial arches. The responsible gene has been mapped to the long arm of chromosome 5 (5q32-q33). It occurs in about 1 in every 10,000 births.

The severity of the clinical changes is variable. Affected individuals exhibit a characteristic facial appearance (Figure 1-65). The zygomas are hypoplastic, resulting in depressed cheeks, downward-sloping lower eyelids, and a narrow face. Seventy-five percent of patients exhibit a notched lower eyelid (*coloboma*). The mandible exhibits condylar and coronoid hypoplasias that present clinically as a retruded chin. The ears exhibit a spectrum of abnormalities, including hypoplastic ear lobes, malformed pinnae, absent ear canals, and defective middle-ear structures with varying degrees of hearing loss, including deafness. **Macrostomia** resulting from unilateral or bilateral facial clefting occurs in about 15% of patients.

Depending on the severity of the developmental defects, surgery may be undertaken for functional and cosmetic reasons.

**FIGURE 1-65**

Treacher Collins syndrome (mandibulofacial dysostosis). Facies exhibiting hypoplasia of zygoma and mandibular condyle resulting in depressed cheeks and a retruded mandible, abnormal ears, downward-sloping lower eyelids, and a narrow face. (Courtesy Dr. Heddie O. Sedano.)

DOWN SYNDROME (TRISOMY 21)

Of all the syndromes, Down syndrome (trisomy 21) is the most common and well known. Its prevalence is approximately one case in 650 live births. The syndrome is the result of chromosomal abnormalities that are manifest as a complex of developmental abnormalities affecting the entire body.

Down syndrome has three genetic types: (1) approximately 95% of cases are of the nondysjunction type that exhibit 47 chromosomes (an extra chromosome 21); (2) approximately 5% of cases result from a translocation of chromosomal material from chromosome 21 to another chromosome; and (3) a small number of cases are the result of chromosomal mosaicism. The prevalence of the common, nondysjunction type of Down syndrome increases with increasing maternal age, especially after 40 years of age.

The common clinical features of individuals with Down syndrome are listed in Box 1-2 (Figure 1-66). In addition, many other less common clinical features have been reported to occur in patients with this syndrome.

Common oral findings include broad lips, an open mouth with protruding tongue, macroglossia, fissured tongue, fissured lips, narrow palate, dental malalignment and malocclusion, congenitally missing teeth, and delayed eruption of both primary and permanent teeth. In 75% of cases, patients have a predisposition to periodontal disease at a young age, increased incidence of

BOX 1-2**Common Clinical Features of Down Syndrome**

Mental retardation
 Short stature
 Brachycephaly
 Short broad neck
 Flat facial profile
 Flat occiput
 Short broad hands
 Thick short fingers
 Single palmar crease
 Small ears with overhanging helices and small or absent earlobes
 Upslanting palpebral fissures
 Epicanthic folds
 Flat nasal bridge
 Hypermobility of joints
 Increased incidence of leukemia and lymphoma

necrotizing ulcerative gingivitis, decreased parotid salivary flow rate, and an apparently low incidence of dental caries.

ORAL-FACIAL-DIGITAL SYNDROME, TYPE I

The oral-facial-digital syndrome, type I (OFD-I) syndrome is an X-linked dominant disorder that occurs only in females (being lethal in males). OFD-I is the result of mutations in the chromosome X open reading frame 5 (CXORF5) gene that has been mapped to the short arm of the X chromosome (Xp22.3-p22.2).

As the name implies, its most obvious abnormalities involve the face, mouth, fingers, and toes. However, the central nervous system and the urinary system are also affected. Mild mental retardation is seen in about 40% of cases.

The distinguishing facial features of the syndrome include frontal bossing, flat midface, lateral displacement of the inner canthi, thin aquiline nose, and pseudocleft of the upper lip. The skeletal features of the syndrome include malformations of the fingers and toes (clinodactyly, syndactyly, brachydactyly), and the short tubular bones of the hands and feet are shorter and thicker than normal.

The oral findings include maxillary clefts of varying severity associated with hyperplastic fibrous frenula. The soft palate is completely and asymmetrically clefted in about 80% of cases. Numerous fibrous bands are present in the mandibular mucobuccal fold in 75% of cases.



FIGURE 1-66

Down syndrome (trisomy 21). Facies exhibiting upslanting palpebral fissures, epicanthic folds, and flat nasal bridge common in this syndrome. (Courtesy Dr. Heddie O. Sedano.)

Cleft tongue with two or more lobules is seen in 30% to 45% of cases.

One or more fibroma-like hamartomatous masses composed of dense fibrous tissue, adipose tissue, some skeletal or smooth muscle fibers, minor salivary gland tissue, and occasionally cartilage are seen in the tongue of 70% of these patients. Diffuse ankyloglossia is seen in approximately 30% of cases. Malpositioned maxillary cuspid teeth and supernumerary deciduous maxillary cuspids and premolars are common. The mandibular lateral incisor teeth are congenitally absent in 50% of cases. The mandible is small or hypoplastic and exhibits short rami.

PAPILLON-LEFÈVRE SYNDROME

Papillon-Lefèvre syndrome is an autosomal recessive disorder characterized by severe destructive periodontal disease affecting both the primary and permanent dentitions and hyperkeratosis of the palms of the hands and soles of the feet. The responsible gene has been mapped to the long arm of chromosome 11 (11q14-21). Parental consanguinity is found in about 40% of cases. Papillon-Lefèvre syndrome appears to represent an immunologic disorder in which various defects in the body's defense system have been reported. Three of these defects are (1) impaired in vitro reactivity to T and B cell mitogens, (2) a chemotactic defect, and (3) reduced intracellular ability to eliminate *S. aureus* and *C. albicans*.

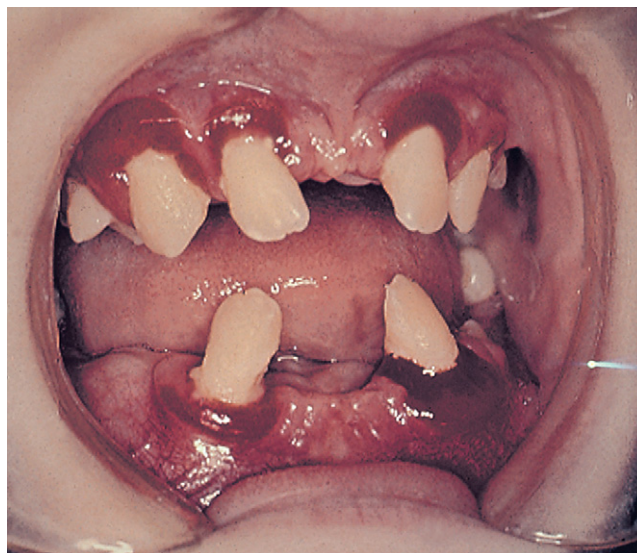
**FIGURE 1-67**

Papillon-Lefèvre syndrome. The skin on the palms (**A**) and soles (**B**) exhibiting diffuse red coloration and scaly patches (palmar and planter keratosis) characteristic of this syndrome.

During the first few years of life, the skin on the palms and soles becomes diffusely red and scaly (Figure 1-67, A and B). The soles are usually more severely affected than the palms. The skin of the knees, elbows, and over the joints of the hands and feet can also be affected. The nails are rarely affected. The development and eruption of the primary teeth proceed normally; however, as the palmar and planter keratosis appears, the gingiva swell, bleed, and become boggy and marked halitosis develops. The destructive periodontitis usually starts after the eruption of the last primary molar tooth.

The severity of the periodontitis follows the order of the tooth eruption (Figure 1-68).

Deep periodontal pocket formation precedes the loss of the teeth. By the age of 4 years, most of the primary teeth are usually lost. After the primary teeth are

**FIGURE 1-68**

Papillon-Lefèvre syndrome. Severe juvenile periodontitis and premature loss of teeth in a 10-year-old female.

**FIGURE 1-69**

Papillon-Lefèvre syndrome. Radiograph exhibiting loss of teeth and extensive loss of alveolar bone.

exfoliated, the gingiva assumes a normal clinical appearance. The gingival appearance remains normal until the permanent teeth erupt, at which time the destructive periodontal disease reappears. Most of the permanent teeth are usually lost by the age of 14 years.

The severe inflammation usually destroys most of the alveolar bone (Figure 1-69). During the destructive inflammatory period, the other oral tissues are unaffected and remain normal.

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2 *Cysts of the Oral Regions*

CHAPTER OUTLINE

ODONTOGENIC CYSTS

- Cysts Derived from Rests of Malassez
 - Periapical Cyst
- Cysts Derived from Reduced Enamel Epithelium
 - Dentigerous Cyst
 - Eruption Cyst
 - Paradental Cyst
- Cysts Derived from Dental Lamina (Rests of Serres)
 - Odontogenic Keratocyst
 - Lateral Periodontal Cyst
 - Gingival Cyst of Adult
 - Dental Lamina Cyst of Newborn
 - Glandular Odontogenic Cyst (Sialo-Odontogenic Cyst)

DEVELOPMENTAL CYSTS OF ORAL REGION

- Cysts of Vestigial Ducts
 - Nasopalatine Duct Cyst
 - Nasolabial Cyst
- Lymphoepithelial Cysts
 - Oral Lymphoepithelial Cyst
 - Cervical Lymphoepithelial Cyst
- Cyst of Vestigial Tract
 - Thyroglossal Tract Cyst
- Cysts of Embryonic Skin
 - Dermoid Cyst
 - Epidermoid Cyst
- Cysts of Mucosal Epithelium
 - Surgical Ciliated Cyst of Maxilla
 - Heterotopic Oral Gastrointestinal Cyst

ADDITIONAL KEY TERMS

- Buccal bifurcation cyst
- Eruption hematoma
- Fissural cyst
- Globulomaxillary radiolucency
- Incisive canal cyst
- Nasoalveolar cyst
- Nevoid basal cell carcinoma syndrome
- Residual cyst
- Rests of dental lamina
- Rests of Serres



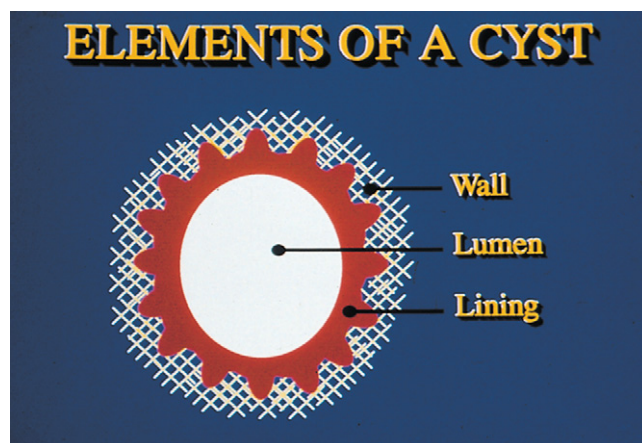


FIGURE 2-1
Elements of a cyst. Wall or capsule, epithelial lining, and lumen.

CYST: A pathologic cavity, lined by epithelium, containing fluid or semisolid material.

A cyst is composed of three basic structures: (1) a central cavity (lumen), (2) an epithelial lining, and (3) an outer wall (capsule) (Figure 2-1). The cystic cavity usually contains fluid or semisolid material such as cellular debris, keratin, or mucus. The epithelial lining differs among cyst types and may be keratinized or nonkeratinized stratified squamous, pseudostratified, columnar, or cuboidal. The cyst wall is composed of connective tissue containing fibroblasts and blood vessels. Cysts often exhibit varying degrees of inflammation that can alter their basic morphology, sometimes obscuring their identifying features. Intense inflammation can destroy some or all of the epithelial lining. In rare instances the entire lining of a cyst may be destroyed by inflammation, allowing it to resolve completely without treatment.

Cysts are common lesions and are clinically important, because they are often destructive. They produce significant signs and symptoms, particularly when they become large or infected.

Most cysts of the oral region are true cysts because they possess an epithelial lining. However, several additional lesions are referred to as *cysts* although they possess no epithelial lining. These *pseudocysts* are lesions such as the traumatic bone cyst, aneurysmal bone cyst, and static bone cyst, which are discussed in Chapters 1 and 4.

The true cysts of the oral region can be divided into those of odontogenic and developmental (nonodontogenic) origin.

ODONTOGENIC CYSTS

ODONTOGENIC CYST: A cyst in which the lining of the lumen is derived from epithelium involved in tooth development.

BOX 2-1

Histogenetic Classification of Odontogenic Cysts

CYSTS DERIVED FROM RESTS OF MALASSEZ

Periapical cyst
Residual cyst

CYSTS DERIVED FROM REDUCED ENAMEL EPITHELIUM

Dentigerous cyst
Eruption cyst
Paradental cyst

CYSTS DERIVED FROM DENTAL LAMINA (RESTS OF SERRES)

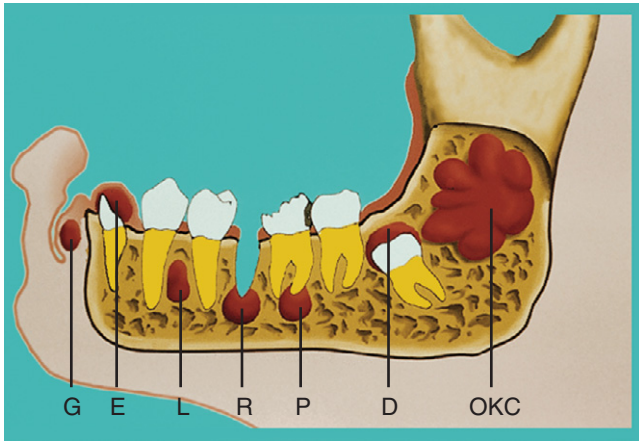
Odontogenic keratocyst (OKC)
Multiple
Lateral periodontal cyst
Polycystic ("botryoid")
Gingival cyst of adult
Dental lamina cyst of newborn
Glandular odontogenic cyst

To facilitate an understanding of the origin and classification of odontogenic cysts, an understanding of odontogenesis is necessary (see Chapter 5). Odontogenic cysts are derived from three epithelial structures: (1) rests of Malassez—remnants of the Hertwig's epithelial root sheath that persist in the periodontal ligament after root formation is complete; (2) reduced enamel epithelium—residual epithelium that surrounds the crown of the tooth after enamel formation is complete; and (3) remnants of the dental lamina (**rests of Serres**)—islands and strands of epithelium that originate from the oral epithelium and remain in the tissues after inducing tooth development. These three sources of odontogenic epithelium represent logical categories on which a histogenetic classification of odontogenic cysts can be based (Box 2-1).

Making an accurate diagnosis of an odontogenic cyst requires information relative to its clinical, radiographic, and histologic findings. In many instances, two cysts that are classified differently may exhibit similar histologic features. In such cases clinical and radiographic findings are necessary to make a precise diagnosis (Figure 2-2).

CYSTS DERIVED FROM RESTS OF MALASSEZ

The rests of Malassez are small islands and strands of odontogenic epithelium found in the periodontal ligament. They represent remnants of Hertwig's root sheath, an embryologic epithelial structure that surrounds a

**FIGURE 2-2**

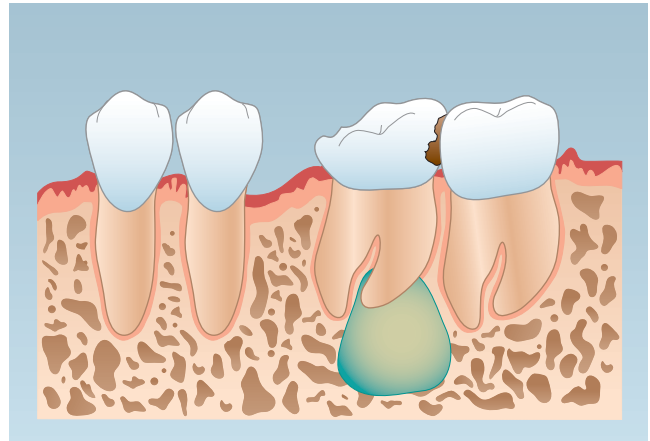
Odontogenic cysts based on typical clinical and radiographic features. Left to right: G, gingival; E, eruption; L, lateral periodontal; R, residual; P, periapical; D, dentigerous; OKC, odontogenic keratocyst. (Modified from McClatchey KD: *Odontogenic lesions: tumors and cysts*. In Batsakis JG: *Tumors of the head and neck*, ed 2, Baltimore, 1979, Lippincott-Williams & Wilkins.)

developing root. Although rests of Malassez are present along the entire length of the root, they are most plentiful at the apical region.

Periapical Cyst

PERIAPICAL CYST: An odontogenic cyst derived from rests of Malassez that proliferate in response to inflammation.

The periapical cyst, also termed *radicular cyst* and *apical periodontal cyst*, is by far the most common type of odontogenic cyst, representing over one half of all oral cysts. It develops at the root apex of an erupted tooth with pulp that has been devitalized by dental caries or trauma (Figure 2-3). The recent decline in the incidence of dental caries has resulted in a corresponding decline in the incidence of periapical cysts. This cyst arises from the rests of Malassez, which enlarge in response to inflammation elicited by bacterial infection of the pulp or in direct response to necrotic pulpal tissue. Because epithelial cells derive their nutrients by diffusion from the adjacent connective tissues, progressive growth of an epithelial island moves the innermost cells of that island away from their nutrients. Ultimately these innermost cells undergo ischemic liquefactive necrosis, establishing a central cavity (lumen) surrounded by viable epithelium. At this point an osmotic gradient is established across the epithelial lining (membrane) separating the connective tissue fluids from the necrotic contents of the newly formed cyst. The net effect of this osmotic gradient is a progressive increase in fluid volume within the lumen,

**FIGURE 2-3**

Periapical cyst.

tending to expand the cyst by the internal hydraulic pressure generated.

CLINICAL FEATURES

Most periapical cysts develop at the apex of a root adjacent to the pulp canal opening. Occasionally they can also develop at the openings of large accessory pulp canals on the lateral aspect of the roots of teeth through which pulpal inflammation and products of pulpal necrosis exit to form granulomas and stimulate the rests of Malassez. These laterally positioned inflammatory cysts have been termed *lateral periapical (radicular) cysts*.

The size of periapical cysts is variable, but generally measure less than 1 cm in diameter. Occasionally the cyst can become much larger, especially in areas where several adjacent teeth of the anterior mandible or maxilla have been devitalized because of facial trauma, commonly the result of an automobile accident.

RADIOGRAPHIC FEATURES

The periapical cyst appears as a rounded, well-circumscribed, often corticated radiolucency at the apex of a nonvital tooth. Cysts that develop on the lateral aspect of the root appear as semicircular radiolucencies against the root surface. Occasionally a periapical cyst that develops in the anterior maxilla in the apical region of a lateral incisor tooth will appear as a **globulomaxillary radiolucency** that may result in divergence of the roots of the lateral incisor and the adjacent cuspid. Histopathologic studies of globulomaxillary radiolucencies indicate that approximately 50% of these radiolucencies are periapical (radicular) cysts. The remaining globulomaxillary radiolucencies represent a spectrum of odontogenic and nonodontogenic lesions that include periapical granuloma, lateral periodontal cyst, odontogenic keratocyst (OKC), central giant cell

granuloma, adenomatoid odontogenic tumor, calcifying odontogenic cyst, odontogenic myxoma, and ameloblastoma.

HISTOPATHOLOGY

A periapical cyst is characterized by a cavity lined with a layer of nonkeratinized squamous epithelium of variable thickness (Figure 2-4, A). These cysts are typically inflamed, and neutrophils are usually present within the epithelial lining. Because the inflammation is often intense, it may destroy part of the epithelial lining, leaving a zone of granulation tissue in its place. The epithelium and occasionally the connective tissues of a small per-

centage (5% to 10%) of odontogenic cysts exhibit collections of laminated crescent-shaped structures termed *hyaline (Rushton) bodies* (Figure 2-4, B). Although these curious structures appear to be unique to odontogenic cysts, they have no known biologic importance. The connective tissue wall of the periapical cyst generally exhibits a significant inflammatory infiltrate consisting of plasma cells, lymphocytes, lipid-laden histiocytes, and neutrophils. Multinucleated giant cells associated with crystalline cholesterol deposits and deposits of hemosiderin are also frequently present in the cyst wall. The cystic lumen usually contains proteinaceous fluid and necrotic cellular debris.

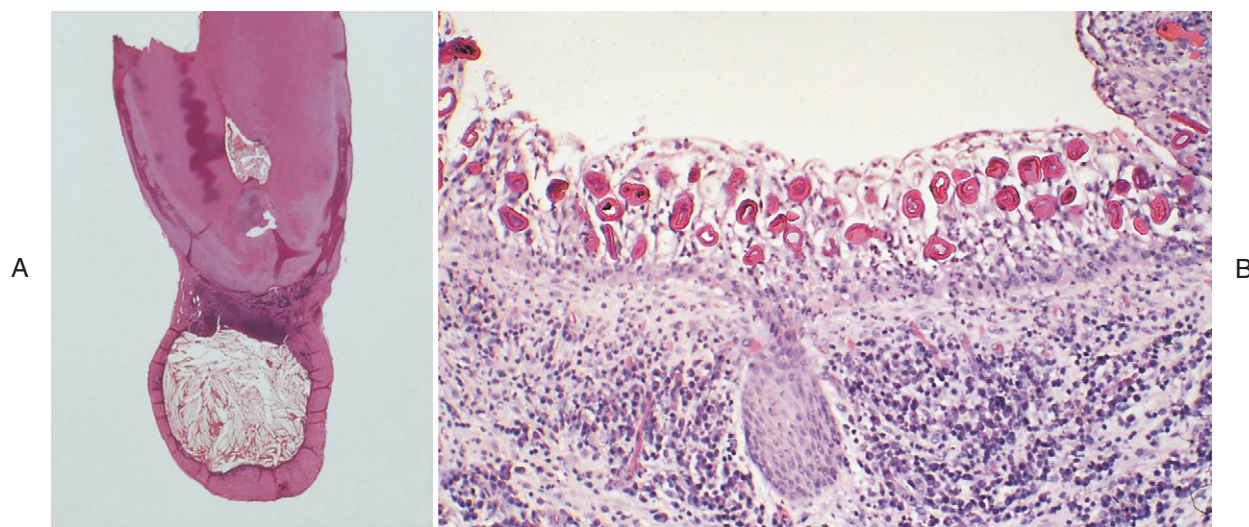


FIGURE 2-4

Periapical cyst. **A**, Carious root fragment with nonvital pulp and periapical cyst attached to apex. **B**, The intraepithelial reddish-colored oval and crescent-shaped structures that occasionally are found are termed *Rushton bodies*.

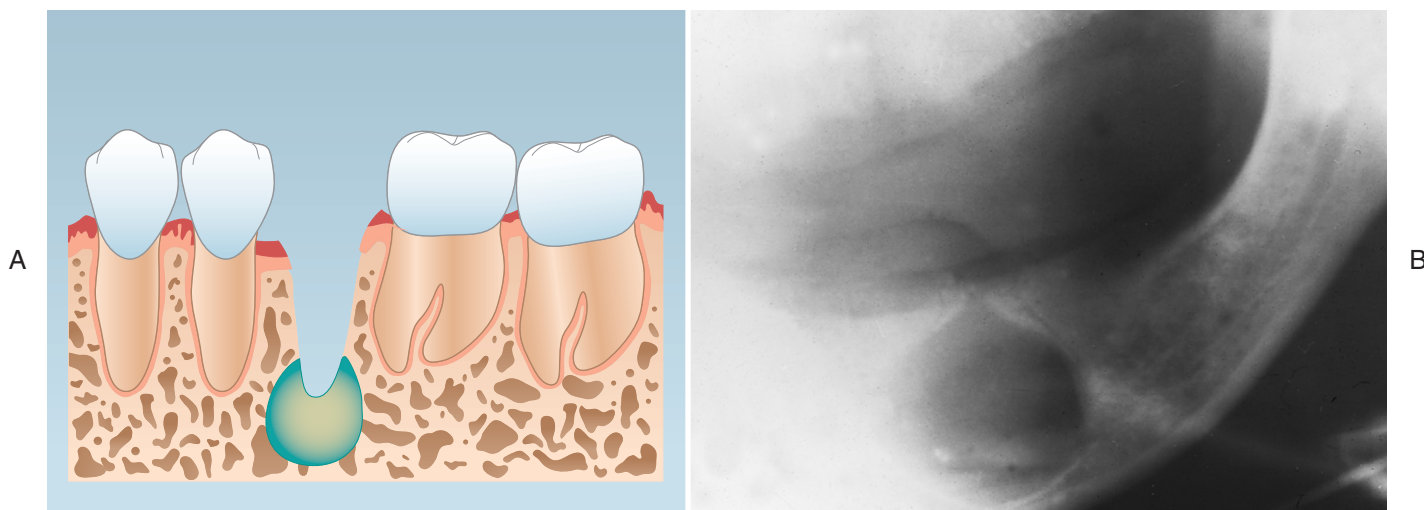


FIGURE 2-5

A, Residual cyst. **B**, Radiograph of residual cyst in an edentulous mandible.

TREATMENT

Treatment of periapical cysts depends on a number of variables. Most of these cysts are treated by enucleation after extraction or endodontic treatment of the offending tooth. Extracting the offending tooth without removing the associated cyst may result in its persistence and continued growth. A cyst that remains at the site of a previously extracted tooth is termed a **residual cyst** (Figure 2-5). Although this is the most common use of the term, it also denotes any cyst present in an edentulous area in which the origin of the epithelial lining is unknown.

CYSTS DERIVED FROM REDUCED ENAMEL EPITHELIUM

Reduced enamel epithelium refers to the layer of epithelium that remains around the tooth's crown after enamel formation is complete. This layer of epithelium is derived from the specialized epithelial components of the enamel organ (inner enamel epithelium, stellate reticulum, outer enamel epithelium) that were active during amelogenesis (enamel formation) and collapses into a thin epithelial membrane of two or three cells in thickness. In addition, the reduced enamel epithelium may include a small population of cells derived from the dental lamina that was connected to the enamel organ during its formation. The reduced enamel epithelium therefore is a complex collection of postsecretory cells with ratios that may differ between teeth and between individuals. Whether the cellular composition of the reduced enamel epithelium affects the growth potential of individual dentigerous cysts is presently unknown.

Dentigerous Cyst

DENTIGEROUS CYST: *An odontogenic cyst that surrounds the crown of an impacted tooth; it is caused by fluid accumulation between the reduced enamel epithelium and the enamel surface, resulting in a cyst in which the crown is located within the lumen and root or roots outside.*

The dentigerous cyst is derived from reduced enamel epithelium that surrounds the crown of an unerupted tooth. Little is known about the stimulus that separates the reduced enamel epithelium from the enamel surface, creating a space for fluid accumulation around the crown of the tooth. These cysts are commonly associated with unerupted mandibular (Figure 2-6) or maxillary third molars or maxillary cuspids. Regardless of its size, the cyst remains attached to the cervical margin of the affected tooth. The crown of the tooth is therefore located within the lumen of the cyst and the root remains outside (Figure 2-7).

CLINICAL FEATURES

A dentigerous cyst usually remains asymptomatic but may produce some swelling or pain, particularly if it is large or inflamed. Because a dentigerous cyst forms around the crown of an impacted or embedded tooth, the arch will clinically appear to be missing at least one tooth.

RADIOGRAPHIC FEATURES

Dentigerous cysts are most commonly diagnosed by their radiographic appearance. They appear as a well-circumscribed radiolucency surrounding the crown of an unerupted tooth (Figure 2-8). The interface with the surrounding bone is corticated, indicative of its slow and uniform growth. In the mandible this cyst may displace the associated tooth inferiorly or superiorly into the ascending ramus. In the maxilla it usually displaces the associated tooth superiorly and posteriorly.

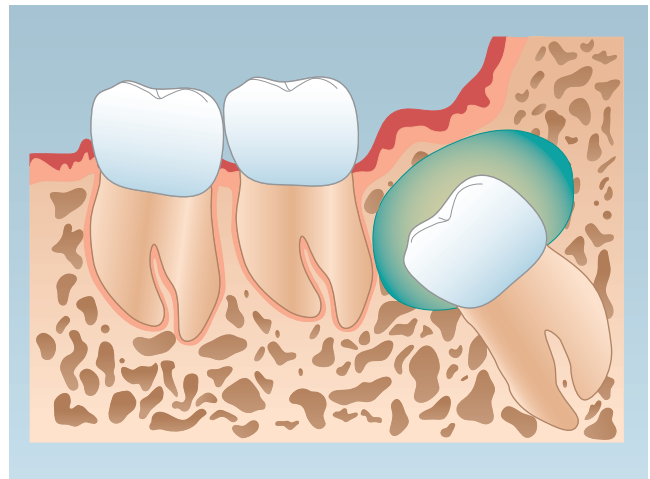
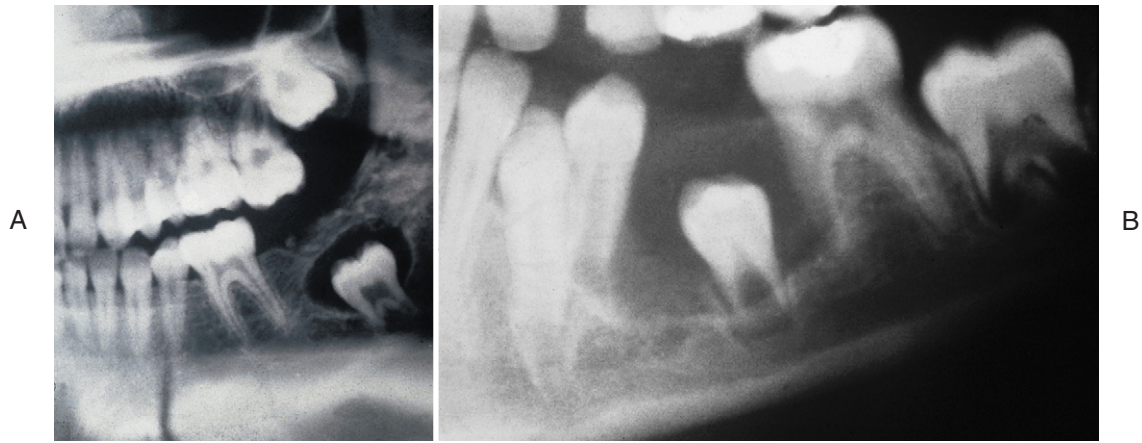


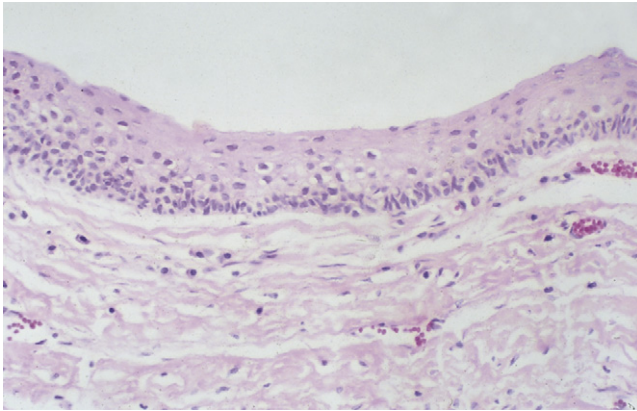
FIGURE 2-6
Dentigerous cyst.



FIGURE 2-7
Dentigerous cyst. Capsule attached at cemento-enamel junction exhibiting the classical appearance of the crown present within the lumen and the roots outside.

**FIGURE 2-8**

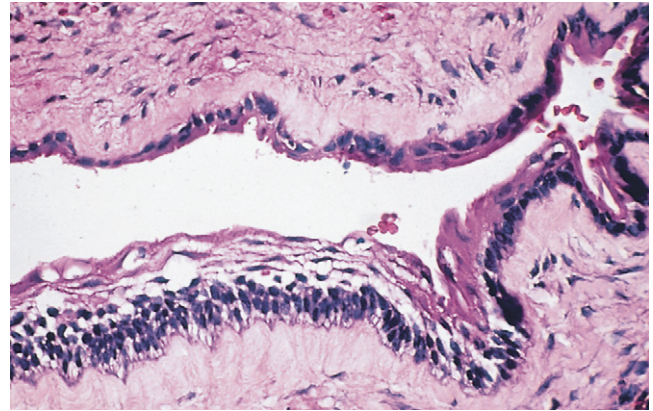
Dentigerous cyst. **A**, Radiograph exhibiting an unerupted molar of the left mandible with a circumscribed radiolucency around the crown. **B**, Radiograph of premolar with dentigerous cyst producing displacement of some of the adjacent teeth.

**FIGURE 2-9**

Dentigerous cyst. Lining exhibiting a thin stratified squamous epithelium without rete peg formation and a capsule of dense fibrous connective tissue.

HISTOPATHOLOGY

The cystic cavity of a dentigerous cyst is lined by a relatively uniform layer of nonkeratinized, stratified, squamous epithelium measuring two to ten cells in thickness (Figure 2-9). Inflammation usually alters the epithelial lining. Depending on the type of inflammation (acute or chronic) and its severity (mild or severe), the epithelial lining may become hyperplastic, atrophic, or ulcerated. In most cases the inflammation is usually a mixture of chronic and acute inflammatory cells. Some of the incidental microscopic features seen in periapical cysts, including crystalline cholesterol deposits, hemosiderin deposits, hyaline (Rushton) bodies, and lipid-laden macrophages are also seen in dentigerous cysts. In addition, variable numbers of mucus cells are

**FIGURE 2-10**

Ameloblastomatous change of lining epithelium of a dentigerous cyst. Such changes are identical to those commonly observed in unicystic ameloblastoma.

occasionally seen in the epithelial lining of this cyst. This finding has been described as either *mucus cell metaplasia* or *mucus cell prosoplasia*. Long-standing dentigerous cysts will occasionally exhibit areas of keratinization or pre-malignant (dysplastic) changes of their epithelial lining.

TREATMENT

Most dentigerous cysts are treated by surgical enucleation. In the case of molar teeth, the associated tooth is usually extracted at the time that the cyst is enucleated. In the case of maxillary cuspid teeth, the cyst may be excised or marsupialized and the tooth brought into proper alignment in the arch with the aid of an orthodontic appliance. Postsurgical recurrence of dentigerous cysts is uncommon. Although it occurs infrequently, several

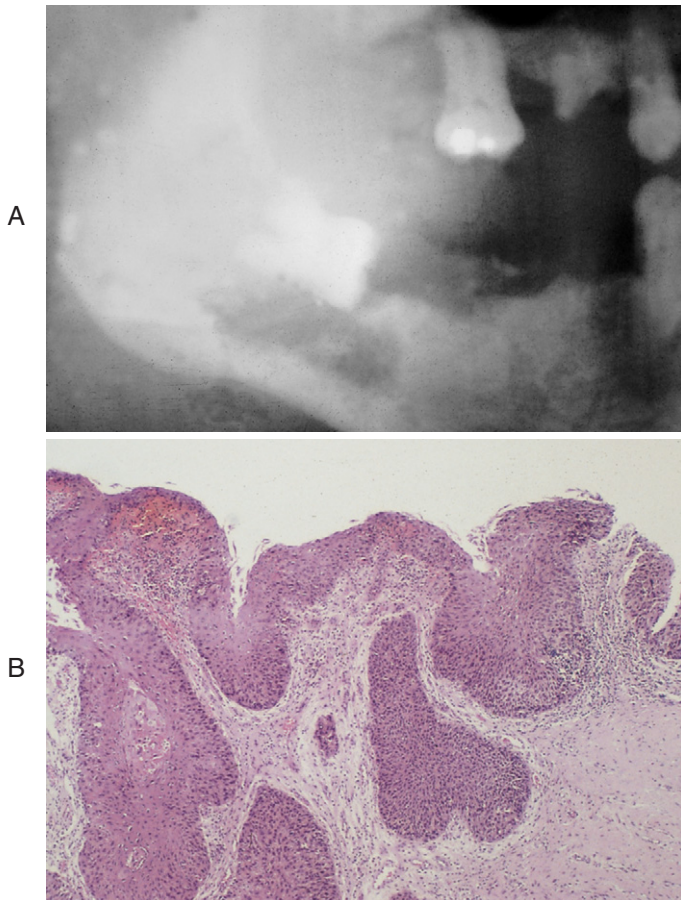


FIGURE 2-11
Squamous cell carcinoma arising in the wall of a dentigerous cyst. Radiographic (A) and microscopic features (B). (From Johnson LM, Sapp JP, McIntire DN: Squamous cell carcinoma arising in a dentigerous cyst, *J Oral Maxillofac Surg* 52:987, 1994.)

different epithelial neoplasms including ameloblastoma (Figure 2-10), mucoepidermoid carcinoma, and squamous cell carcinoma (Figure 2-11) can arise in dentigerous cysts. Under such circumstances the cyst and its associated neoplasm would usually require more aggressive treatment to eradicate the neoplasm.

Eruption Cyst

ERUPTION CYST: An odontogenic cyst with the histologic features of a dentigerous cyst that surrounds a tooth's crown that has erupted through bone but not soft tissue and is clinically visible as a soft fluctuant mass on the alveolar ridges.

The eruption cyst is a variant of the dentigerous cyst that develops in the alveolar soft tissue around the crown of an erupting tooth (Figures 2-12 and 2-13, A). Because this cyst is largely confined to soft tissues, it is clinically

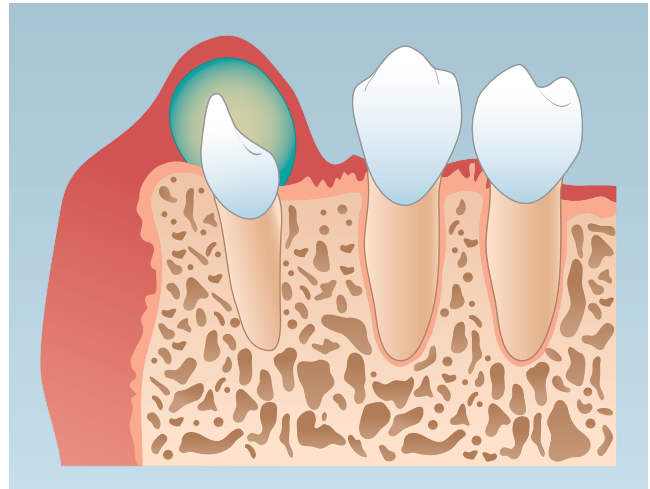


FIGURE 2-12
Eruption cyst.

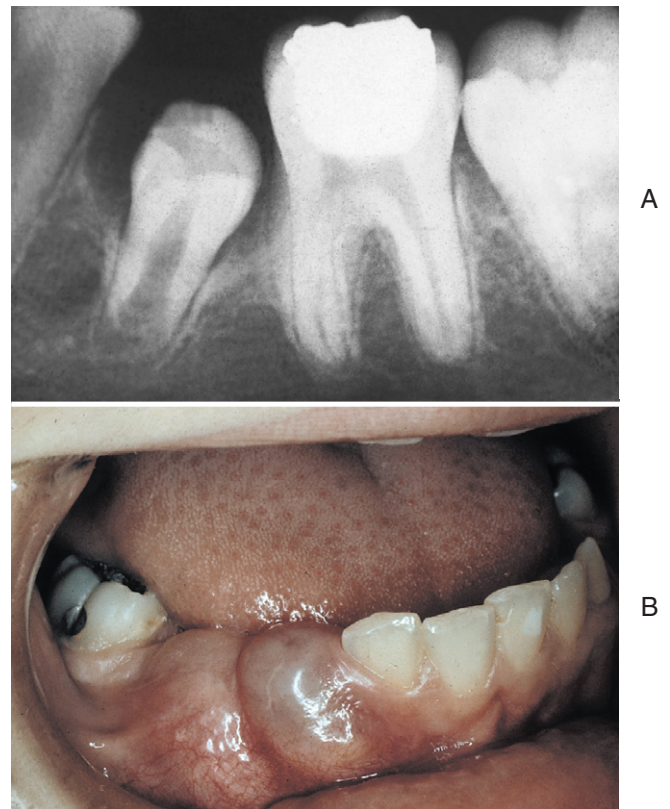


FIGURE 2-13
Eruption cyst. A, Radiograph of a partially erupted premolar. B, Clinical appearance of fluctuant soft tissue masses of lesions overlying two erupted premolars.

evident as a fluctuant swelling of the alveolar ridge (Figure 2-13, B) rather than as an intrabony radio-lucency. Mastication will occasionally induce hemorrhage in an eruption cyst, giving rise to the term **eruption hematoma**

for this cyst. The cyst is derived from the reduced enamel epithelium, and its histologic features are essentially the same as those of a dentigerous cyst. Variable numbers of ghosted epithelial cells, derived from exfoliated lining cells, are often seen within the organizing hemorrhage that may be present in the lumen of these cysts. Most of these cysts require no treatment, because they spontaneously rupture and become exteriorized as a result of normal mastication. For those eruption cysts that do not resolve spontaneously, the crown of the involved tooth can be surgically exposed, simultaneously treating the cyst and allowing the involved tooth to erupt.

Paradental Cyst

PARADENTAL CYST: A cyst of odontogenic origin commonly located subgingivally on the buccal aspect of an erupted mandibular molar (bifurcation cyst) or the distal surface of a partially erupted mandibular third molar.

The paradental cyst is an odontogenic cyst located on the buccal or distal aspect of a tooth, usually a mandibular molar. It appears that there may be more than one pathogenesis for this clinical entity. When located on the buccal aspect of a molar tooth (usually a first or second molar) overlying the bifurcation area and upper portion of the root, it has been termed a **buccal bifurcation cyst**, or less commonly a *Craig cyst*. The buccal bifurcation cyst usually contains inflammatory cells in the cyst capsule, although the mandibular molar is vital. It is believed to arise from the reduced enamel epithelium (sulcular epithelium). A particularly significant predisposing factor for many is that the crown of the associated tooth exhibits an anomaly known as *cervical enamel projection* (see Chapter 1). Once cyst formation is initiated, apical extension below the usual cemento-enamel junction into the bifurcation area and beyond ensues. The presence of the cyst and the associated inflammation in such a superficial intraosseous location in young patients may induce a reactive periosteal proliferation or localized form of Garré's osteomyelitis that resolves when the cyst is removed. Other theories for the development of a buccal bifurcation cyst suggest that it arises from stimulated odontogenic rests in and around the furcation area or that it arises because the tooth fails to quickly attain a state of full eruption. In the latter, it is postulated that the partially erupted tooth becomes stalled for a period leaving the margin of the free gingiva above the height of contour on the buccal surface of the crown. This allows for continuous impaction of food particles and bacteria into the sulcus resulting in an inflamed deep and enlarged pocket or paradental cyst that eventually extends to and beyond the bifurcation area.

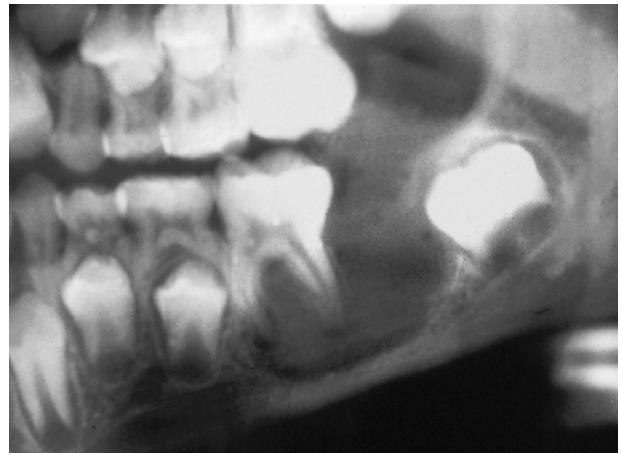


FIGURE 2-14

Radiograph of a paradental cyst associated with a vital mandibular left permanent first molar.

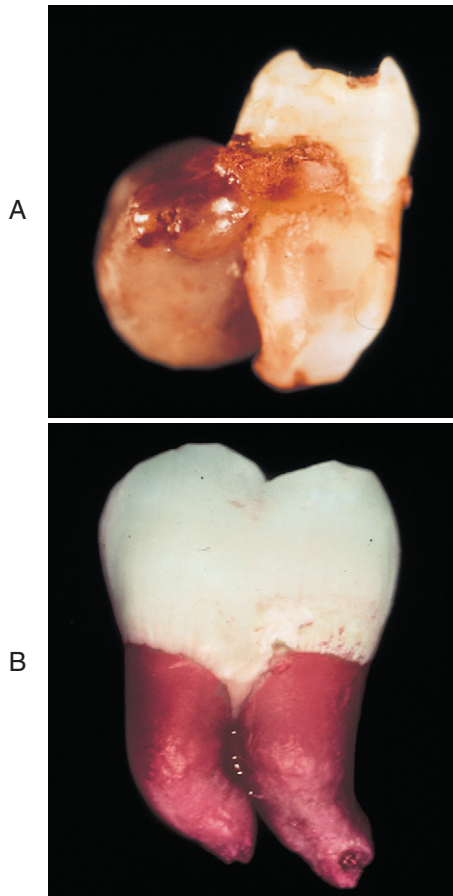
Another form of paradental cyst associated with a deep pocket periodically occurs on the distal of a mandibular third molar, particularly when the tooth is anatomically impeded by the ascending ramus. Usually the mesial cusps are exposed and mucosa or bone overlies the distal cusps. In such cases a deep distal pocket may develop within the ramus and over time result in a cyst or cystlike lesion. In still other situations, a true cyst with no communication with the oral cavity develops on the root portion of a tooth apical to the cemento-enamel junction. Although the cause is still unclear, such cysts are noninflammatory and have sometimes been referred to as *distally displaced dentigerous cysts*. A possible cause is that these cysts arise from odontogenic rests that are in close proximity to the distal of the tooth.

RADIOGRAPHIC FEATURES

A paradental cyst that develops on the buccal aspect of a mandibular molar may not be visible in routine radiographs, because its image is superimposed on the associated tooth (Figures 2-14 and 2-15, A). A paradental cyst that involves the distal aspect of a molar tooth, especially a mandibular third molar, is readily apparent as a well-circumscribed radiolucency in routine periapical or panoramic radiographs. The cervical enamel projection (Figure 2-15, B) is seldom visible on routine dental radiographs.

HISTOPATHOLOGY

The paradental cyst is lined by a hyperplastic layer of nonkeratinized squamous epithelium that is usually infiltrated by varying numbers of neutrophils; its connective tissue capsule is chronically inflamed. The histopathologic

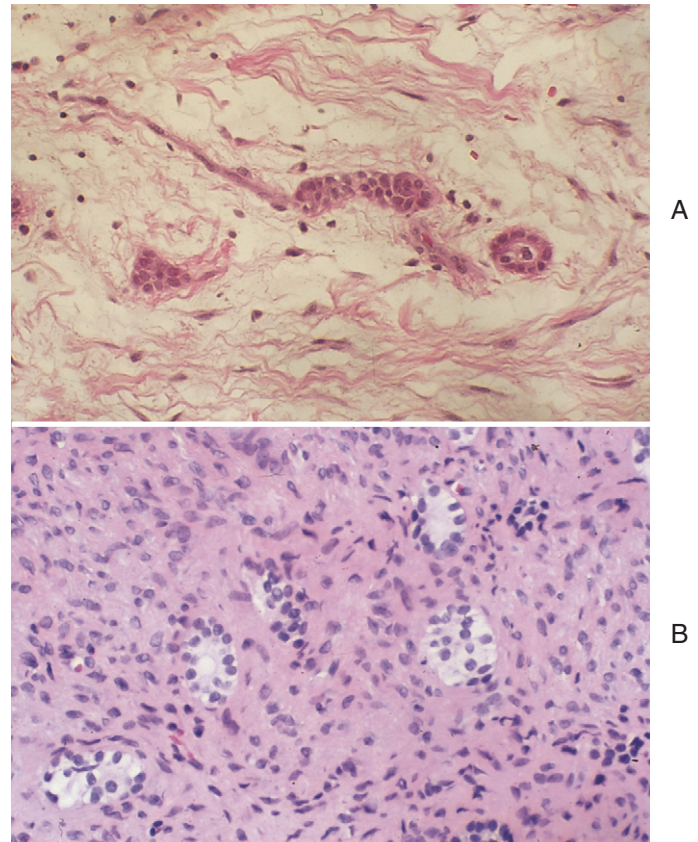
**FIGURE 2-15**

A, Paradental cyst attached to the buccal aspect of a vital mandibular first permanent molar. **B**, Cervical enamel projection extending into the buccal bifurcation area of a mandibular second molar that had a paradental cyst over this area. The overlying cyst has been removed and the tooth stained with eosin to accentuate the cementoenamel interface.

features of a paradental cyst resemble those of an inflamed dentigerous cyst and without clinical and radiographic correlation may be diagnosed as such by the pathologist.

TREATMENT

The paradental cyst is usually treated by surgical enucleation. Because the exact nature of the lesion is usually not recognized at the time of treatment, the associated molar tooth is often inappropriately extracted as part of the surgical procedure. As the ability to recognize (clinically and radiographically) various forms of paradental cysts before treatment improves, treatment of lesions without extracting the associated molar tooth should become possible. The distally located paradental cyst of mandibular third molars is usually included with removal of the impacted molar.

**FIGURE 2-16**

Rests of the dental lamina. A, Common form. **B**, Less common clear cell variant (rests of Serres).

CYSTS DERIVED FROM DENTAL LAMINA (RESTS OF SERRES)

The dental lamina is an embryologic strand of epithelium that carries the dental organ to its destination within the developing fetal jaws. During its functional period, the dental lamina connects the developing enamel organ to the alveolar mucosa. In its postfunctional period, the dental lamina becomes disrupted into a series of small islands and strands of epithelium that are termed **rests of dental lamina** (Figure 2-16, A). These rests persist into adulthood and can be found in the gingival connective tissue and within the underlying alveolar bone. Generally the rests exhibit features of squamous cells, but some accumulate significant amounts of glycogen that impart a clear or transparent appearance to their cytoplasm. The clear cell rests of dental lamina are termed *rests of Serres*. Although the two forms of the rests of the dental lamina are technically different, both names are commonly used interchangeably (Figure 2-16, B).

Odontogenic Keratocyst

ODONTOGENIC KERATOCYST: A cyst derived from the remnants (rests) of the dental lamina, with a biologic behavior similar to a benign neoplasm, with a distinctive lining of six to ten cells in thickness, and that exhibits a basal cell layer of palisaded cells and a surface of corrugated parakeratin.

The OKC is derived from remnants of the dental lamina. The OKC can develop at virtually any site in the jaws, with approximately two thirds of the cases occur-

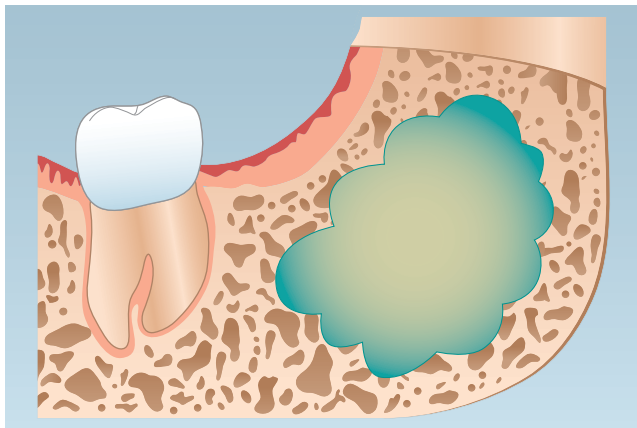


FIGURE 2-17
Odontogenic keratocyst.

ring in the mandible, primarily in the posterior body and ramus areas (Figure 2-17). Occasionally, the OKC develops around the crown of an unerupted tooth, in a true dentigerous cyst relationship. Some authors have postulated that OKC that are present in a true dentigerous cyst relationship have undergone fusion with a pre-existing dentigerous cyst. Although the OKC usually presents as a single lesion, it can occasionally occur as multiple cysts that sometimes occupy all four quadrants of the jaws. The OKC possesses a remarkable growth potential, greater than the other odontogenic cysts, and can attain a large size resulting in massive bone destruction (Figure 2-18, A). Lesions of the maxilla occur primarily in the posterior segment or in the cuspid-lateral incisor area (Figure 2-18, B). The OKC exhibits a recurrence rate of 25% to 60%, similar to that of an ameloblastoma. In this respect the OKC differs significantly from the other odontogenic cysts. Although the majority of OKCs are intraosseous lesions, on very rare occasions they are extraosseous, occurring entirely within the gingival soft tissues. These rare extraosseous OKCs have been termed *peripheral OKCs*.

CLINICAL FEATURES

OKCs occur over a wide age range, from the first to the eighth decades of life; the peak incidence is during the second and third decades of life. Multiple OKCs are a consistent feature of the **nevroid basal cell carcinoma syndrome** (Gorlin-Goltz syndrome) (Figure 2-19). Patients who exhibit multiple OKCs should therefore be appropriately ex-

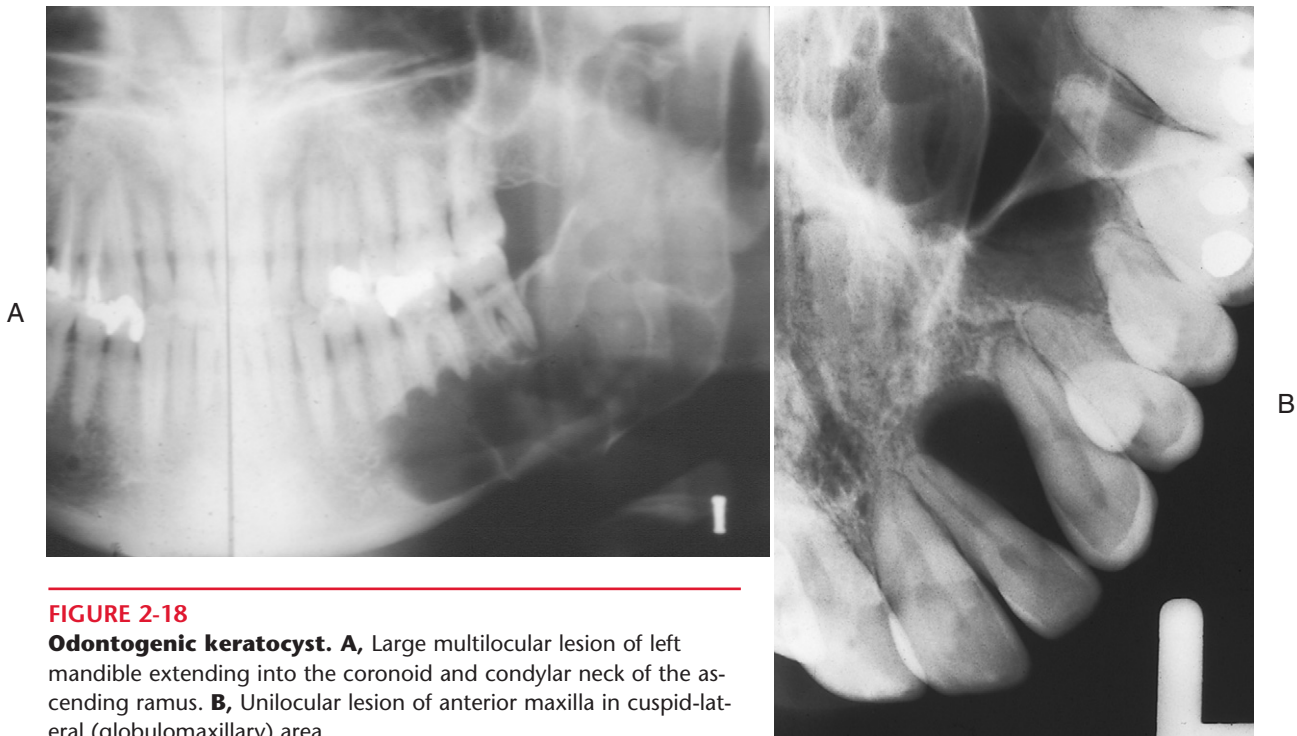
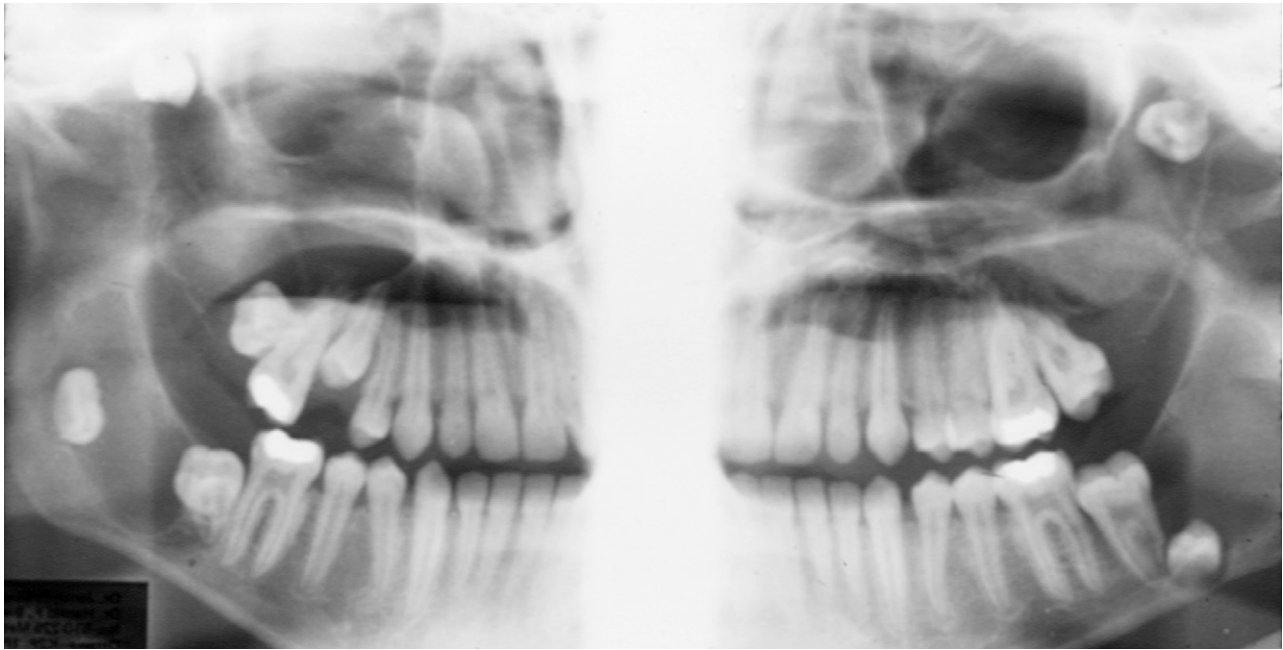


FIGURE 2-18
Odontogenic keratocyst. **A**, Large multilocular lesion of left mandible extending into the coronoid and condylar neck of the ascending ramus. **B**, Unilocular lesion of anterior maxilla in cuspid-lateral (globulomaxillary) area.

**FIGURE 2-19**

Nevoid basal cell carcinoma syndrome. Reveals multiple odontogenic keratocysts. Lesions are present in the posterior of all four quadrants with displaced unerupted molars.

amined to rule out this autosomal dominant syndrome. Predominant features of this syndrome, in addition to multiple OKC, are bifid ribs, nevoid basal cell carcinomas, calcification of the falx cerebri (Figure 2-20, A), multiple small epidermoid cysts (milia) (Figure 2-20, B), frontal bossing, shortened metacarpals (Figure 2-20, C), and medulloblastoma (Box 2-2).

RADIOGRAPHIC FEATURES

The OKC will appear as a well-defined, solitary lesion with smooth or scalloped margins or as a multilocular, polycystic radiolucency exhibiting a thin corticated margin. The corticated appearance of this cyst will usually be obscured if the cyst is inflamed or has perforated the cortex of the involved bone.

HISTOPATHOLOGY

The microscopic appearance of OKCs is distinctive. It has four characteristics: (1) a thin, uniform lining of parakeratinized squamous epithelium, usually 6 to 10 cells thick; (2) a palisaded layer of columnar or cuboidal basal cells; (3) a corrugated (rippled) layer of parakeratin on its luminal surface; and (4) a lack of rete pegs. Commonly the cyst exhibits focal separation of the epithelial lining from the adjacent connective tissue that is often loose and fibrillar and usually free of inflammation. The cystic lumen contains variable amounts of desquamated parakeratin. Additional features that are occasionally

BOX 2-2

Predominant Features of the Nevoid Basal Cell Carcinoma Syndrome

Multiple odontogenic keratocysts of jaws	Multiple epidermoid cysts (milia) of skin
Multiple basal cell carcinomas of skin	Frontal bossing
Bifid ribs	Hypertelorism
Calcification of the falx cerebri	Ovarian fibromas
Palmar and plantar dyskeratosis	Other
	Medulloblastoma
	Shortened metacarpals

seen include remnants of dental lamina (odontogenic rests), microcyst formation, satellite (daughter) cysts, epithelial budding from basal cell area, and a lining composed of orthokeratinized rather than parakeratinized epithelium (Figure 2-21). A summary of these features is outlined in Box 2-3.

TREATMENT

The usual treatment of the OKC is surgical enucleation. In cases where extensive perforation of the mandible has occurred, surgical resection has occasionally been used. Recently, there has been an increased interest in

**FIGURE 2-20****Nevoid basal cell carcinoma syn-**

drome. Features include calcification of the falx cerebri (A), forehead exhibiting frontal bossing with skin "milia" (B), and shortened metacarpals (C).

marsupialization of the very large lesions to reduce their size before surgical removal. Preliminary results have been encouraging in reducing morbidity and the need for extensive rehabilitative reconstruction. Despite the skill of the surgeon, recurrences of this cyst can be expected, and the patient should be advised that more than one procedure might be required to eradicate the cyst. Although

most recurrences will become apparent within the first 5 years after surgical removal, they may occasionally recur as long as 10 years later. Close clinical follow-up of the surgical site is therefore advisable. A notable exception to the relatively high recurrence rate of this cyst is the uncommon orthokeratinized variant of OKC that has a much lower recurrence rate (less than 5%).

BOX 2-3**Histologic Features of Odontogenic Keratocysts**

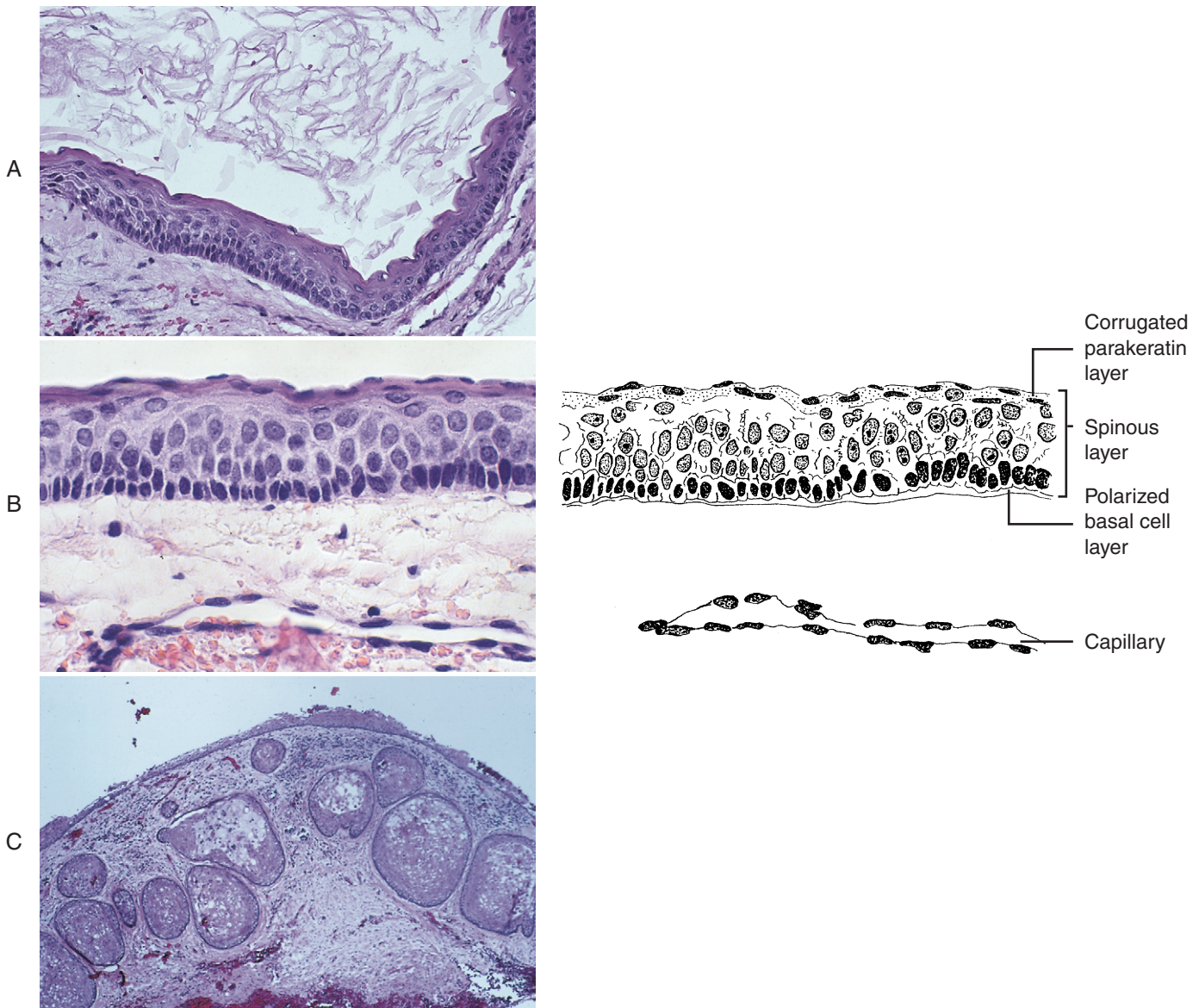
- Thin uniform lining of parakeratinized squamous epithelium of 6 to 10 cells
- Corrugated parakeratin on the luminal surface
- Lack of rete peg formation
- Focal separation of epithelial lining from the connective tissue
- Lumen containing variable amounts of desquamated parakeratin
- Dental lamina rests and microcysts occasionally present in capsule wall
- Generally lacks inflammatory response in capsule

Lateral Periodontal Cyst

LATERAL PERIODONTAL CYST: A slow-growing, non-expansile developmental odontogenic cyst derived from one or more rests of the dental lamina, exhibiting a lining of one to three cuboidal cells and distinctive focal thickenings (plaques).

CLINICAL FEATURES

The lateral periodontal cyst is a relatively uncommon odontogenic cyst that shares a striking number of clinical and morphologic similarities with the gingival cyst of the adult. These similarities have led to the conclusion that the lateral periodontal cyst and the gingival cyst of the adult respectively represent the intraosseous and extraosseous manifestations of the same lesion,

**FIGURE 2-21**

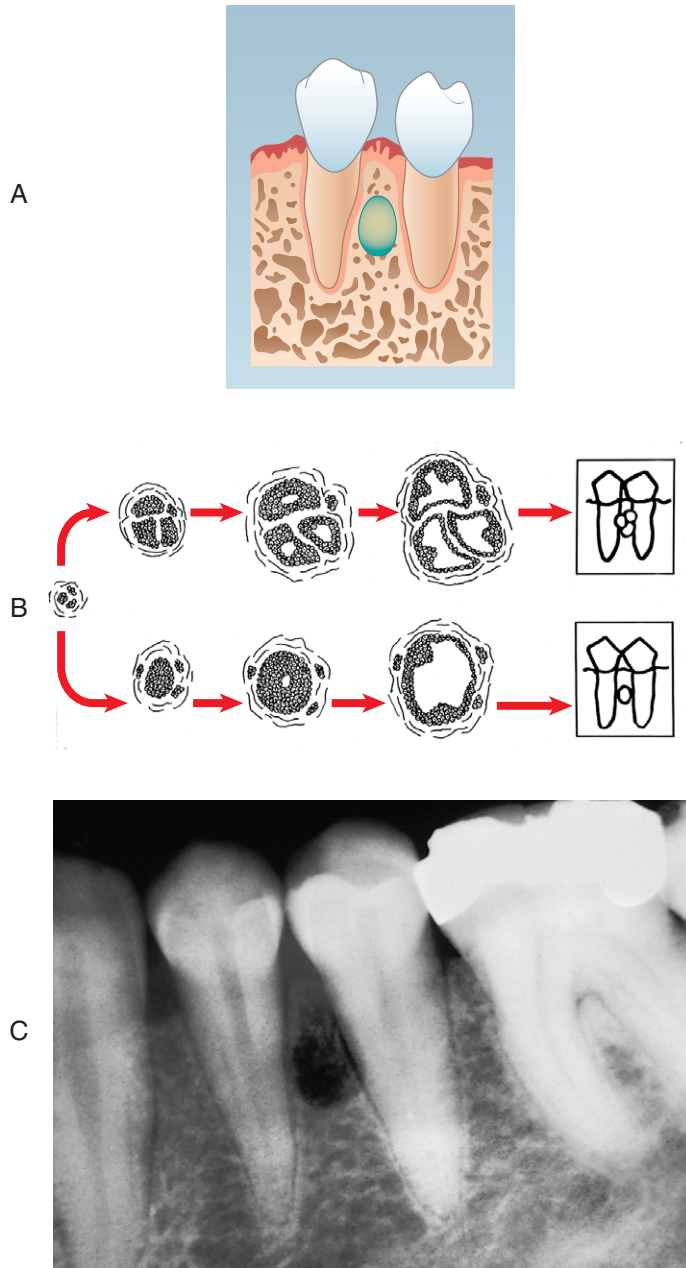
Odontogenic keratocyst. Low (**A**) and high (**B**) magnification of thin epithelial lining (6 to 10 cells) exhibiting the keratin-filled lumen, corrugated parakeratinizing surface, and palisaded basal cell layer that lacks rete peg formation and displays a delicate, loose connective tissue capsule. **C**, Capsule wall containing satellite (daughter) cysts.

both being derived from rests of the dental lamina (rests of Serres). The lateral periodontal cyst usually develops as a solitary lesion, presumably from a single odontogenic rest. On occasion, multiple rests may simultaneously become cystic, resulting in a cluster of lesions (Figure 2-22, A and B).

RADIOGRAPHIC FEATURES

The lateral periodontal cyst is usually seen as a small, well-defined, delicately corticated, unilocular radiolucency located between the roots of vital teeth (Fig-

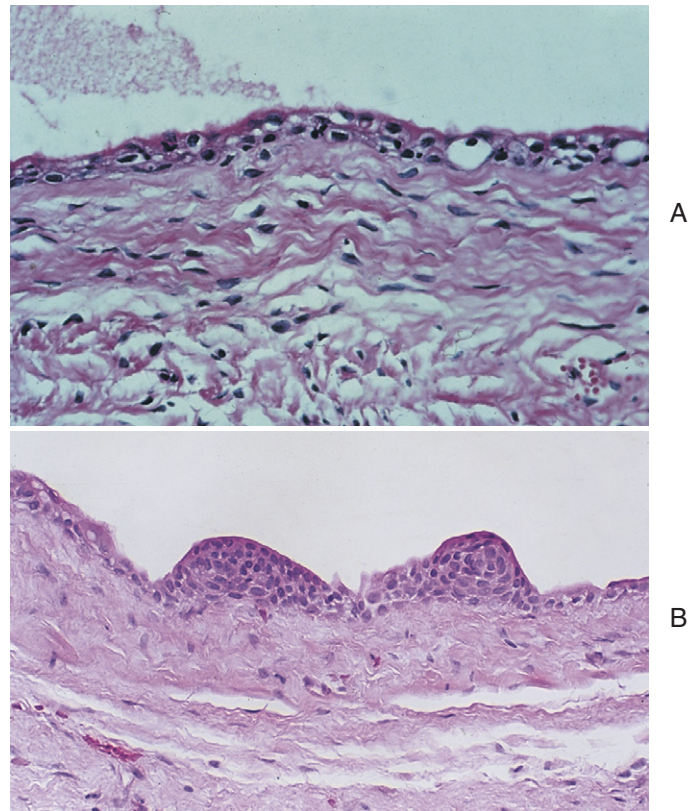
ure 2-22, C). The lesion is usually less than 1 cm in diameter and is most commonly found in the mandibular premolar region, often between the two premolars (see Figure 2-22, B) and, in the anterior maxilla between the cuspid and lateral incisor. However, it can occur between any of the anterior teeth of the mandible or maxilla. The mean age of occurrence of this cyst is in patients who are approximately 50 years old. The rare, polycystic (botryoid) variant of the lateral periodontal cyst may be seen as a multilocular radiolucency.

**FIGURE 2-22**

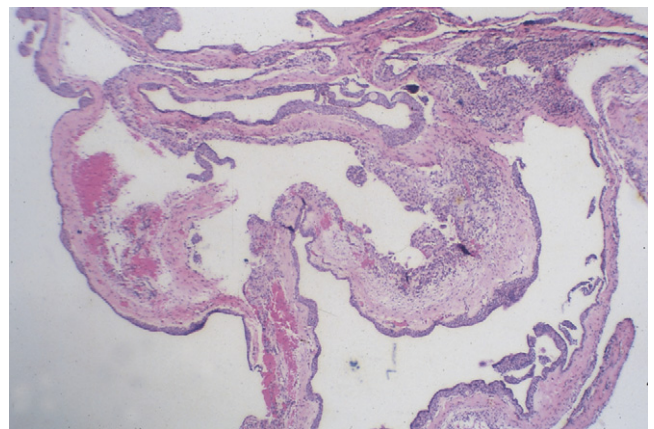
A, Lateral periodontal cyst. **B**, A unicystic and a polycystic (botryoid) lateral periodontal cyst developing from rests of dental lamina and their respective radiographic appearance. **C**, Radiograph of small lesion in premolar-cuspid area.

HISTOPATHOLOGY

The typical histologic features include a thin lining of nonkeratinized epithelium measuring one to three cells in thickness, with variable numbers of glycogen-rich clear cells (Figure 2-23, A). Some of these cysts exhibit focal epithelial thickenings (plaques) (Figure 2-23, B) that exhibit cellular features seen in rests of Serres. In

**FIGURE 2-23**

Lateral periodontal cyst. **A**, Epithelial lining consisting of cuboidal cells with occasional clear cells. **B**, Lining containing focal thickenings (plaques).

**FIGURE 2-24**

Lateral periodontal cyst. Polycystic variant or "botryoid odontogenic cyst."

addition, rests of Serres in various stages of cyst formation can occasionally be seen in the wall of this cyst. This cyst is derived from dental lamina rests.

Although most lateral periodontal cysts are unicystic, they can occasionally be polycystic (Figure 2-24). This polycystic variant was originally described as the “botryoid odontogenic cyst.”

TREATMENT

The treatment for lateral periodontal cyst is surgical enucleation. Recurrence is uncommon.

Gingival Cyst of Adult

GINGIVAL CYST OF THE ADULT: *A small developmental odontogenic cyst of the gingival soft tissue derived from the rests of the dental lamina, exhibiting a lining of squamous to cuboidal epithelium with occasional distinctive focal thickenings similar to those seen in the lateral periodontal cyst.*

The gingival cyst of the adult develops in the gingival soft tissues outside of bone (Figure 2-25) and is derived from the rests of the dental lamina (rests of Serres), the same rests that give rise to the lateral periodontal cyst. The gingival cyst of the adult is, in all respects, the soft tissue equivalent of the lateral periodontal cyst.

CLINICAL FEATURES

The gingival cyst of the adult occurs as a firm but compressible, fluid-filled swelling on the mandibular or maxillary facial gingiva in the premolar, cuspid, and incisor region (Figure 2-26). The clinical distribution, clinical size, age of occurrence, and histologic features of the gingival cyst of the adult are strikingly similar to those of the lateral periodontal cyst. For these reasons it has been concluded that these two cysts represent the extraosseous and intraosseous manifestations of the same entity.

RADIOGRAPHIC FEATURES

Most gingival cysts of the adult are confined to the gingival soft tissues and are therefore not apparent on radiographs. Occasionally, however, they will cause a pressure-induced depression (saucerization) in the underlying alveolar bone that is sometimes apparent on radiographic examination.

HISTOPATHOLOGY

Lesions are often small, with the epithelial lining closely resembling the lining of the lateral periodontal cyst (Figure 2-27, A). It is thin, usually two to five cells in thickness, and often exhibits mural thickenings (plaques) (Figure 2-27, B). As in the lateral periodontal cyst, clear cells may be present.

TREATMENT

This cyst is easily treated with conservative surgical enucleation and has no tendency to recur.



FIGURE 2-25
Gingival cyst of the adult.

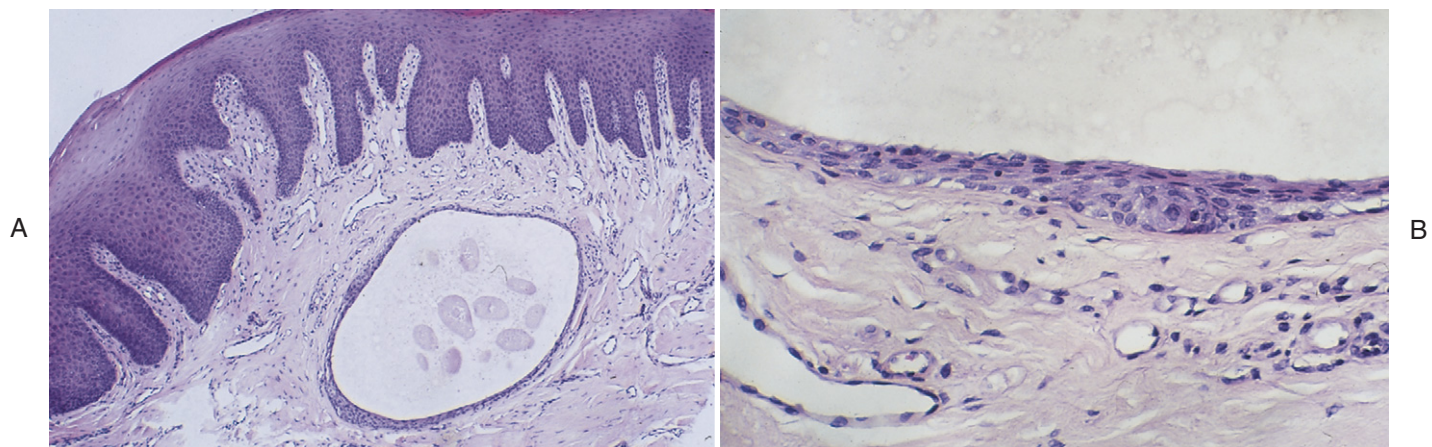


FIGURE 2-26
Gingival cyst of the adult. Lesion of the gingiva in the premolar-cuspid area.

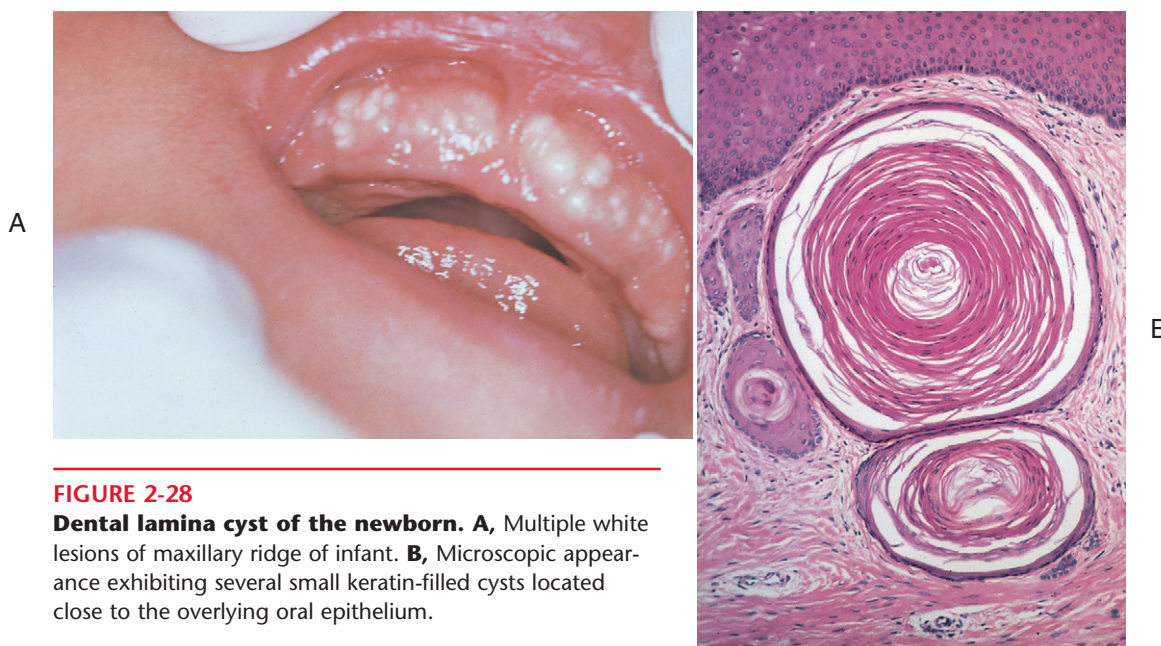
Dental Lamina Cyst of Newborn

DENTAL LAMINA CYST OF NEWBORN: *Small, sometimes multiple, raised cystic nodules that occur on the alveolar ridges of infants; they are derived from rests of the dental lamina and consist of a keratin-filled cystic cavity.*

The dental lamina cyst of the newborn, as the name indicates, is derived from the remnants (rests) of the dental lamina that remain in the soft tissues of the jaws. The cysts are generally seen on the alveolar ridges of newborn infants as small, often multiple swellings (Figure 2-28, A). The microscopic appearance consists of a superficially located thin-walled cystic lesion lined by a

**FIGURE 2-27**

Gingival cyst of the adult. Small lesion of gingiva **(A)** with lining containing focal thickening (plaque) similar to lateral periodontal cyst **(B)**.

**FIGURE 2-28**

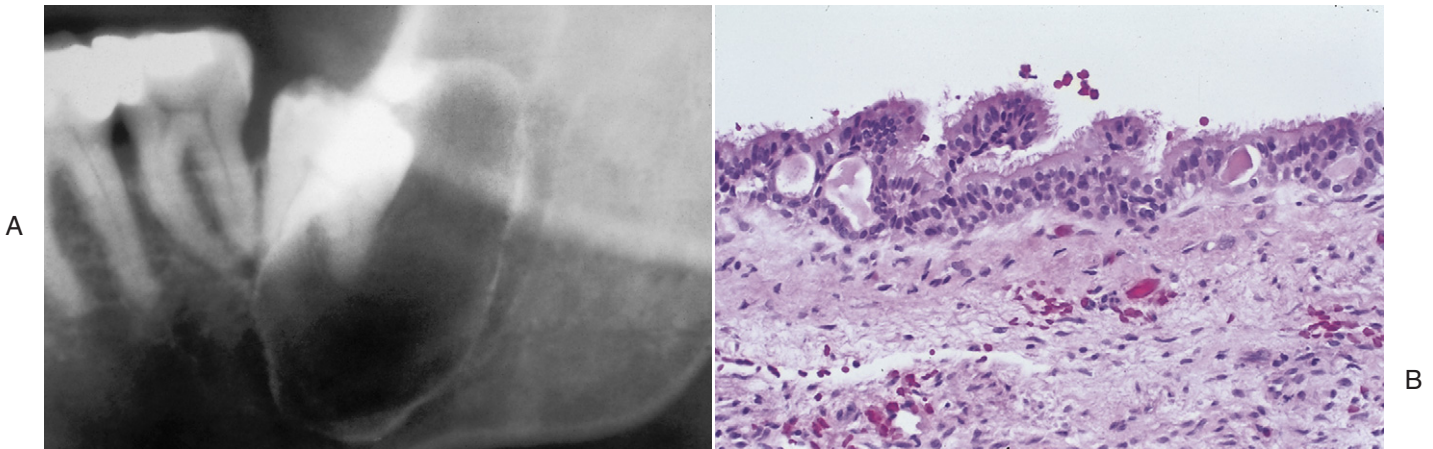
Dental lamina cyst of the newborn. **A**, Multiple white lesions of maxillary ridge of infant. **B**, Microscopic appearance exhibiting several small keratin-filled cysts located close to the overlying oral epithelium.

thin, stratified, squamous epithelium, and containing compacted desquamated keratin (Figure 2-28, B). Because these cysts usually resolve spontaneously in response to normal function, they require no treatment. It is of interest to note the remarkable difference in the age occurrence between the dental lamina cyst of the newborn and the gingival cyst of the adult, both of which are generally agreed to arise from dental lamina. The disparity in age of occurrence between these two cysts is probably best explained by the likelihood that the two cysts arise from different dental lamina, respectively, the

primary dental lamina, which is more superficial, than the *permanent dental lamina*.

Glandular Odontogenic Cyst (Sialo-Odontogenic Cyst)

GLANDULAR ODONTOGENIC CYST: A unilocular or multilocular odontogenic cyst derived from the rests of dental lamina and characterized by a lining with variable numbers of small intraepithelial glandular structures lined by cuboidal or columnar cells, often including mucus cells.

**FIGURE 2-29**

A, Glandular odontogenic cyst presenting as a well-circumscribed radiolucency in the posterior mandible of a 69-year-old male. **B**, Thin lining exhibiting cuboidal and columnar cells with intraepithelial microcysts containing mucoid secretion.

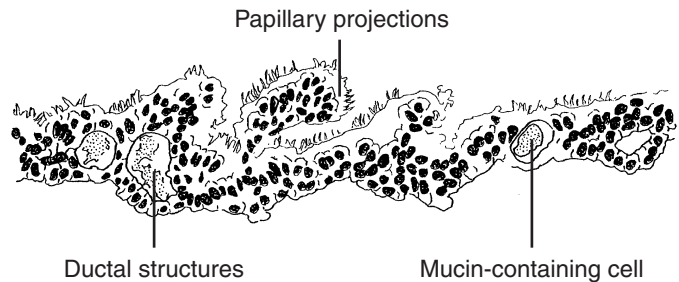
The glandular odontogenic cyst was first described in 1987. It was originally termed a “sialo-odontogenic cyst.” Because the histologic features in some examples of this cyst closely resemble those seen in the polycystic variant of lateral periodontal cyst (botryoid odontogenic cyst), both are considered to arise from dental lamina. Although the glandular odontogenic cyst shares some features with the lateral periodontal cyst, it also exhibits some distinctly different features. It exhibits a much greater growth potential than the lateral periodontal cyst and has some propensity to recur, thus justifying its classification as a separate entity.

RADIOGRAPHIC FEATURES

The glandular odontogenic cyst occurs primarily, but not exclusively, in the mandible. The radiographic appearance is not specific, with lesions commonly being large (Figure 2-29, A). Cysts may appear as well-defined, unilocular, or multilocular radiolucencies.

HISTOPATHOLOGY

Three histologic features typify this unusual cyst: (1) a thin squamous epithelial lining that may be relatively uniform in thickness or may exhibit focal epithelial thickenings (plaques, eddies); (2) variable numbers of small glandular structures or microcysts within the lining epithelium; and (3) a single layer of columnar or cuboidal cells lining the glandular structures, replacing the surface layer of the stratified squamous epithelium



of the cyst lining. The glandular spaces contain variable amounts of PAS-positive and mucicarmine-positive secretory product. Occasionally, mucus cells resembling goblet cells of the intestinal mucosa and ciliated cells are also present (Figure 2-29, B).

TREATMENT

Cases have been treated by surgical enucleation and curettage. Some of these lesions have been large and polycystic, and recurrences have been reported.

DEVELOPMENTAL CYSTS OF ORAL REGION

The term **fissural cyst** is still often used for cysts derived from epithelium present during embryonic development, but it is now considered a misnomer. Until recently it was thought that some cysts of the jaws developed from epithelium that became entrapped along embryologic lines of closure (fissures). Current thought is that epithelial entrapment does not occur in these sites during embryogenesis. As a result some of the previously held concepts of cyst formation have been modified, and terms such as “globulomaxillary cyst” and “median mandibular cyst” have been largely abandoned. The two developmental cysts that remain in this category are not of fissural derivation; they are (1) the nasopalatine duct cyst (**incisive canal cyst**) and (2) the nasolabial cyst.

CYSTS OF VESTIGIAL DUCTS

Nasopalatine Duct Cyst

NASOPALATINE DUCT CYST: *An intraosseous developmental cyst of the midline of the anterior palate, derived from the islands of epithelium remaining after closure of the embryonic nasopalatine duct.*

The nasopalatine duct cyst, also termed incisive canal cyst, arises from embryologic remnants of the nasopalatine duct. Most of these cysts develop in the midline of the anterior maxilla near the incisive foramen (Figure 2-30). Although most are intraosseous lesions, a small percentage develop at the lower end of the incisive canal entirely

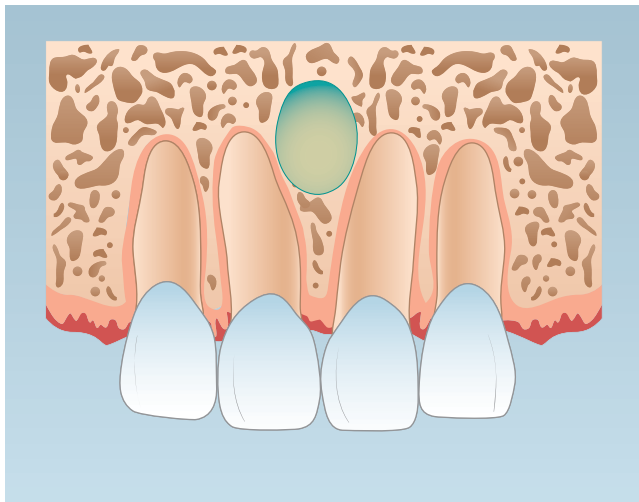


FIGURE 2-30
Nasopalatine duct cyst.



FIGURE 2-31
Nasopalatine duct cyst. Occlusal radiograph of anterior maxilla with a well-demarcated oval-shaped radiolucency of the midline extending between the roots of the central incisors.

within the soft tissue of the anterior palate and are termed cysts of the incisive papilla. On rare occasion, the nasopalatine duct remains patent and persists into adult life as small unilateral or bilateral openings on the palatal mucosa adjacent to the incisive papilla.

RADIOGRAPHIC FEATURES

The nasopalatine duct cyst presents as a well-circumscribed oval or heart-shaped radiolucency located in the midline of the anterior maxilla between the roots of the central incisors (Figure 2-31). In the edentulous maxilla the radiographic diagnosis may not be as obvious as in the dentate patient. Although some of these cysts are asymptomatic and discovered during routine radiographic examination, many are inflamed and cause pain, pressure, and swelling. Cysts of the incisive papilla are entirely within the palatal soft tissues and are not evident radiographically.

HISTOPATHOLOGY

These cysts are lined by a layer of ciliated columnar (respiratory), cuboidal, or stratified squamous epithelium or by a mixture of these epithelial types (Figure 2-32). If inflammation is present, it usually consists of an infiltrate of plasma cells and lymphocytes. The cyst capsule typically exhibits the prominent component of blood vessels and peripheral nerves that comprise normal incisive canal contents. The presence of these neurovascular elements can be helpful in reaching a microscopic diagnosis. In addition, occasional small lobules of salivary type mucus glands may be seen in the cyst wall. Premalignant or malignant transformation of the epithelial lining in this cyst has not been reported. The histologic features of the cyst of the incisive papilla closely resemble those of the nasopalatine duct cyst.

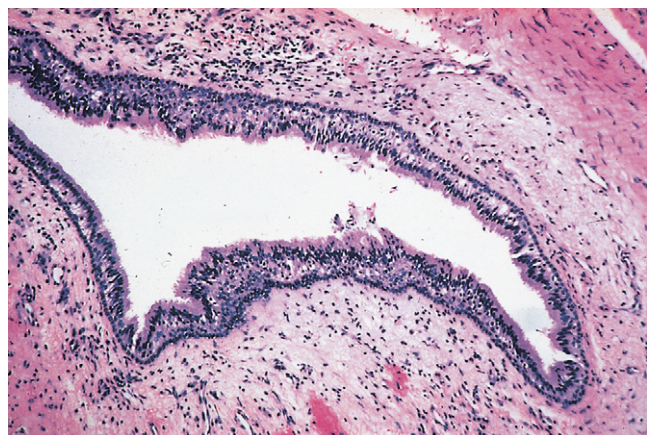


FIGURE 2-32
Nasopalatine duct cyst. A cyst lined by respiratory-type epithelium surrounded by a fibrous capsule exhibiting a mild degree of chronic inflammation.

TREATMENT

Treatment of the nasopalatine duct cyst is by surgical enucleation, using a palatal approach. Recurrence of this cyst is rare.

Nasolabial Cyst

NASOLABIAL CYST: A developmental cyst of the soft tissue of the anterior mucobuccal fold beneath the ala of the nose, most likely derived from remnants of the inferior portion of the nasolacrimal duct.

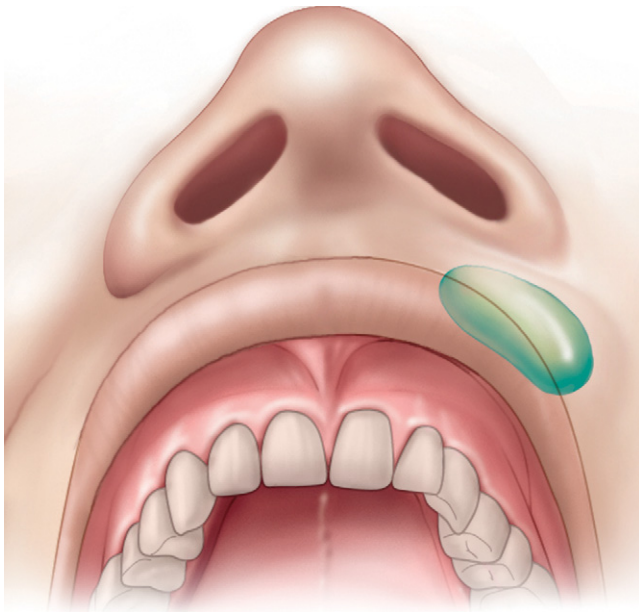


FIGURE 2-33
Nasolabial cyst.

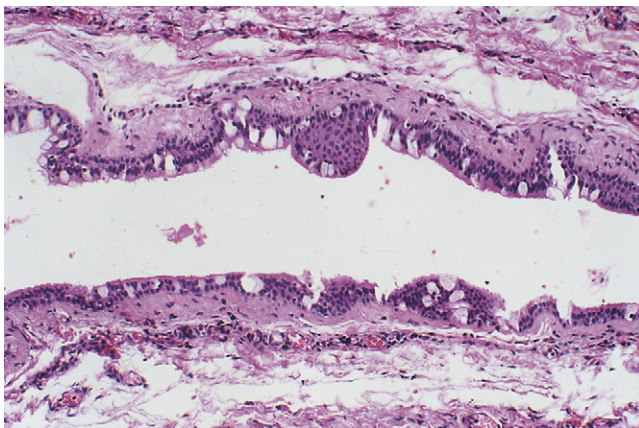


FIGURE 2-34
Nasolabial cyst. Microscopic features exhibiting loose connective tissue surrounding a lumen lined with ciliated pseudostratified columnar epithelium containing mucus (goblet) cells.

Also known as the **nasoalveolar cyst** and the **Klestadt cyst**, this rare condition occurs entirely in the soft tissues of the anterior maxillary vestibule, below the ala of the nose and deep in the nasolabial crease (Figure 2-33). Although other theories for the development of this rare cyst have been previously proposed, the most plausible and currently accepted thought points to its derivation from remnants of the inferior and anterior portions of the nasolacrimal duct.

CLINICAL FEATURES

This cyst is a unilateral or occasionally bilateral painless soft tissue swelling that results in a flattening of the nasolabial crease on the skin below the ala of the nose. If the upper lip is appropriately retracted, this cyst also can be seen intraorally as a swelling located at the depth of the maxillary vestibule. Most of these cysts occur in the fourth and fifth decades of life and have a female predilection of approximately 3 to 1.

Because this cyst is located entirely within soft tissue, it is not readily apparent radiographically unless contrast medium is injected into the cystic lumen to facilitate visualization. Focal pressure-induced bone resorption (saucerization) of the anterior maxilla can be occasionally demonstrated on radiographs and is most readily seen in the edentulous patient.

HISTOPATHOLOGY

The cyst is lined by a layer of pseudostratified columnar epithelium exhibiting variable numbers of mucus (goblet) cells or by a ductal type of cuboidal epithelium (Figure 2-34). A lining of stratified squamous epithelium can be seen in some lesions. Some degree of folding of the cyst lining and of the associated connective tissue is often seen. A narrow zone of dense, homogeneous, fibrous tissue is usually seen adjacent to the epithelial lining. Inflammation is generally absent.

TREATMENT

A nasolabial cyst is treated by surgical enucleation with particular care being exercised to prevent the lesion's perforation and collapse. Recurrence is rare.

LYMPHOEPITHELIAL CYSTS

LYMPHOEPITHELIAL CYST: A cyst with a lumen lined by a keratinizing stratified squamous epithelium and a capsule containing multiple normal lymphoid follicles and a dense accumulation of normal lymphocytes.

Lymphoepithelial cysts are relatively uncommon lesions that occur in several areas of the head and neck, most commonly in the floor of the mouth and on the lateral aspect of the neck. Those occurring intraorally are termed *oral lymphoepithelial cysts*, and those occur-

ring on the lateral aspect of the neck are termed *cervical lymphoepithelial cysts*. Although cysts in the oral cavity are considerably smaller than those on the lateral aspect of the neck, their histopathologic features are essentially the same.

Oral Lymphoepithelial Cyst

ORAL LYMPHOEPITHELIAL CYST: A lymphoepithelial cyst commonly located intraorally on the posterior lateral tongue and the anterior floor of the mouth.

The oral lymphoepithelial cyst, also termed *benign lymphoepithelial cyst*, most commonly develops where extratonsillar lymphoid tissue (oral tonsil) is found. The most common sites are the anterior floor of the mouth and the posterior lateral border of the tongue. It appears to develop from epithelial invaginations (crypts) that become detached from the surface mucosa and entrapped within the lymphoid tissue; cyst formation ensues. An alternate theory suggests that the epithelium in these cysts could be derived from minor salivary ducts that traverse oral lymphoid tissue.

CLINICAL FEATURES

The oral lymphoepithelial cyst is most commonly found on the anterior floor of the mouth (Figure 2-35) and on the posterior lateral borders of the tongue. However, it can also occur on the ventral surface of the tongue, soft palate, tonsillar pillars, and oropharynx. It is an asymptomatic, yellowish or tan, superficial submucosal mass that usually measures less than 1 cm in diameter. Careful clinical examination of the oral mucosa overlying these cysts or gross examination of the excised lesional tissue will occasionally reveal a small pore or crypt that communicates with the cyst's lumen.

HISTOPATHOLOGY

The cyst is lined by a relatively thin layer of parakeratinized squamous epithelium surrounded by a well-defined mass of normal lymphoid tissue exhibiting variable numbers of germinal centers (Figure 2-36). The cystic lumen is usually filled with desquamated parakeratin. Occasionally, the pore or crypt that communicates between the surface mucosa and the cystic lumen can be seen microscopically. The presence of bacteria within the cystic lumen in some of these cysts is also evidence that communication with the oral cavity is present.

TREATMENT

Treatment of these cysts is by conservative surgical excision. The lesion seldom recurs.



FIGURE 2-35

Oral lymphoepithelial cyst. Lesion of floor of mouth.

Cervical Lymphoepithelial Cyst

CERVICAL LYMPHOEPITHELIAL CYST: An unusually large lymphoepithelial cyst located on the lateral aspect of the neck.

The cervical lymphoepithelial cyst, also commonly termed *branchial cleft cyst* or *benign cystic lymph node*, occurs on the lateral aspect of the neck, usually anterior to the sternocleidomastoid muscle. It is thought to be derived from epithelium entrapped within lymphoid tissues of the neck during embryologic development of the cervical sinuses or the second branchial clefts or pouches. An alternate theory suggests that the epithelium in this cyst might be derived from salivary duct epithelium trapped within cervical lymph nodes during embryogenesis.

CLINICAL FEATURES

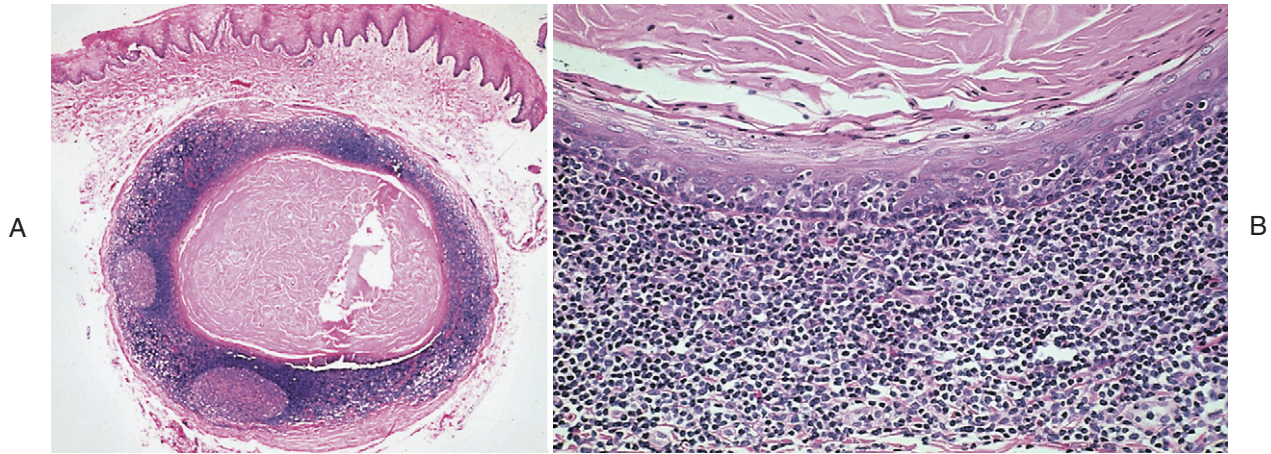
The cyst becomes apparent in late childhood or early adulthood as a painless swelling on the lateral aspect of the neck anterior to the sternomastoid muscle (Figure 2-37). A draining fistula that communicates between the cyst and the overlying skin surface occasionally develops.

HISTOPATHOLOGY

The cyst lumen is usually lined by a thin layer of stratified squamous epithelium and contains desquamated orthokeratin. The capsule wall is thickened, consisting of a fibrous connective tissue containing large numbers of well-formed lymphoid follicles (Figure 2-38).

TREATMENT

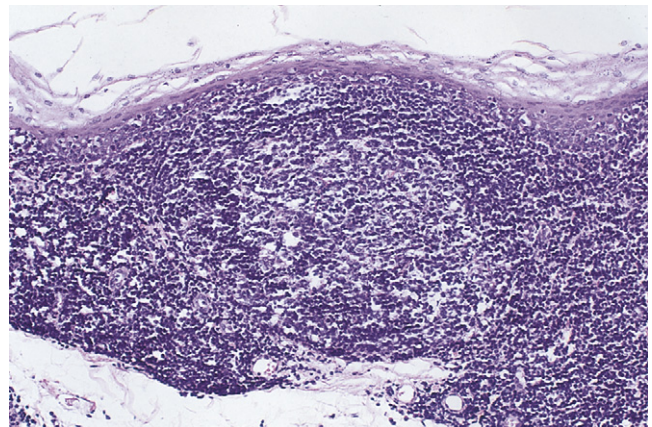
As with its intraoral counterpart, the cervical lymphoepithelial cyst is treated by conservative surgical excision; recurrence is rare.

**FIGURE 2-36**

Oral lymphoepithelial cyst. **A**, Low magnification of photomicrograph of keratin-filled cyst surrounded by lymphoid follicles from the anterior floor of the mouth. **B**, Higher magnification exhibiting a thinned squamous epithelium, keratin in the lumen, and surrounded by a dense zone of lymphocytes.

**FIGURE 2-37**

Cervical lymphoepithelial cyst. Lesion on left lateral neck.

**FIGURE 2-38**

Cervical lymphoepithelial cyst. A portion of the cyst wall lined by keratinizing squamous epithelium and containing lymphoid tissue.

CYST OF VESTIGIAL TRACT

Thyroglossal Tract Cyst

THYROGLOSSAL TRACT CYST: A cyst located above the thyroid gland and beneath the base of the tongue, with a lumen lined by a mixture of epithelial cell types derived from remnants of the embryonic thyroglossal tract and often containing thyroid tissue in the capsule.

The thyroglossal tract cyst is a relatively uncommon lesion derived from embryologic remnants of the thyroglossal tract. This tract extends from the foramen caecum on the middorsum of the tongue to the thyroid gland. Although these cysts can develop anywhere along the length of this tract, 70% to 80% occur below the hyoid bone, where the tract makes two distinct turns on its descent to the thyroid gland.

CLINICAL FEATURES

This cyst occurs primarily in children and young adults and presents as an asymptomatic, slowly enlarging, mobile swelling involving the midline of the anterior neck

above the thyroid gland (Figure 2-39). A small percentage of these cysts occur within the tongue, where they can cause dysphagia. If infected or inflamed, a draining fistula that communicates between the cyst and the overlying skin surface will occasionally develop.

HISTOPATHOLOGY

This cyst is lined by stratified squamous epithelium, ciliated columnar epithelium, transitional epithelium, or a mixture of epithelial types. The cyst capsule can exhibit a number of additional findings including lymphoid aggregates, thyroid tissue (Figure 2-40), mucus glands, and sebaceous glands. Carcinoma can occasionally develop from the lining of thyroglossal tract cysts and from remnants of the thyroglossal tract.



FIGURE 2-39
Thyroglossal tract cyst. Lesion located on midline of anterior neck.

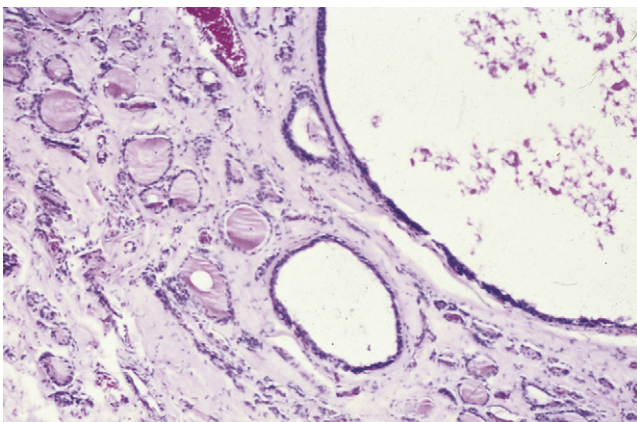


FIGURE 2-40
Thyroglossal tract cyst. Microscopic features reveal thyroid tissue in cyst wall.

TREATMENT

The treatment of the thyroglossal tract cyst requires complete surgical excision, because recurrence is a distinct possibility. In an effort to minimize recurrence of cysts involving the hyoid area, it is recommended that the central portion of the hyoid bone and its associated remnants of thyroglossal tract be removed.

CYSTS OF EMBRYONIC SKIN

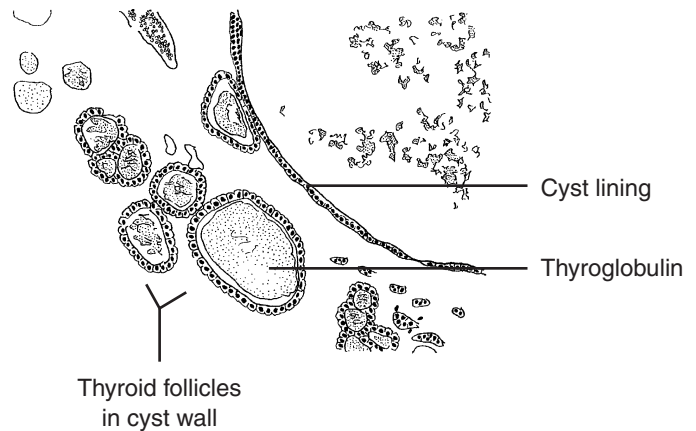
Dermoid Cyst

DERMOID CYST: A cyst of the midline of the upper neck or the anterior floor of the mouth of young patients, derived from remnants of embryonic skin, consisting of a lumen lined by a keratinizing stratified squamous epithelium, and containing one or more skin appendages such as hair, sweat, or sebaceous glands.

The dermoid cyst represents a simple form of cystic teratoma derived from germinal epithelium entrapped during embryonic development. Most of these cysts occur in the head and neck region, primarily in the skin around the eyes and the anterior upper neck, extending superiorly into the floor of the mouth.

CLINICAL FEATURES

The dermoid cyst is a lesion of young adults (teenagers). No gender predilection is seen. Cysts of the anterior upper neck or floor of the mouth present as painless swellings exhibiting a doughy consistency on palpation. Cysts that develop above the mylohyoid muscle present as a midline swelling in the sublingual (floor of the mouth) area. In this location the cyst results in elevation of the tongue and can interfere with eating and speaking. Cysts that develop below the



mylohyoid muscle (Figure 2-41, A) appear as a mid-line swelling in the submandibular and submental region. The size of these cysts is variable, but most are 2 cm or less in diameter.

HISTOPATHOLOGY

A layer of orthokeratinized squamous epithelium exhibiting variable numbers of dermal appendages, including hair follicles, sebaceous glands, and associated erector pili muscles lines the cyst. The cystic lumen is generally filled with a mixture of desquamated keratin, sebum, and hair shafts. The cyst capsule is composed of a narrow zone of compressed connective tissue that is generally free of inflammation (Figure 2-41, B).

TREATMENT

This cyst is best treated by surgical enucleation or excision. Recurrence is uncommon.

Epidermoid Cyst

EPIDERMOID CYST: A cyst of skin with a lumen lined by keratinizing stratified squamous epithelium, usually filled with keratin and without skin appendages in the capsule wall.

The epidermoid cyst occurs primarily on skin. However, occasional cysts of the oral cavity exhibit the histopathologic characteristics of epidermoid cysts. The epidermoid cyst closely resembles a dermoid cyst, except that the former exhibits no dermal appendages. They are lined by orthokeratinized squamous epithelium and exhibit a lumen that is generally filled with desquamated keratin (Figure 2-42). The cyst wall consists of a narrow zone of compressed fibrous connective tissue that is generally free of inflammation. This cyst is treated by surgical enucleation or excision. Recurrence is uncommon.

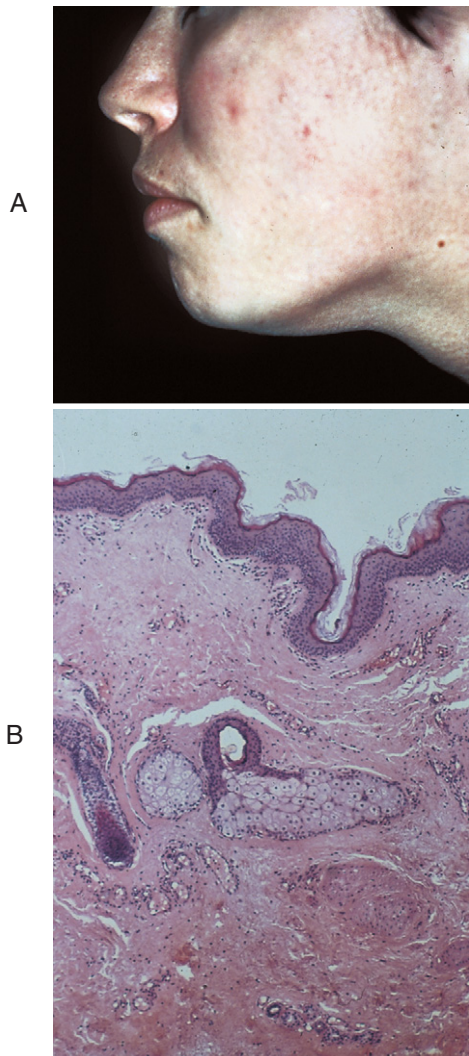
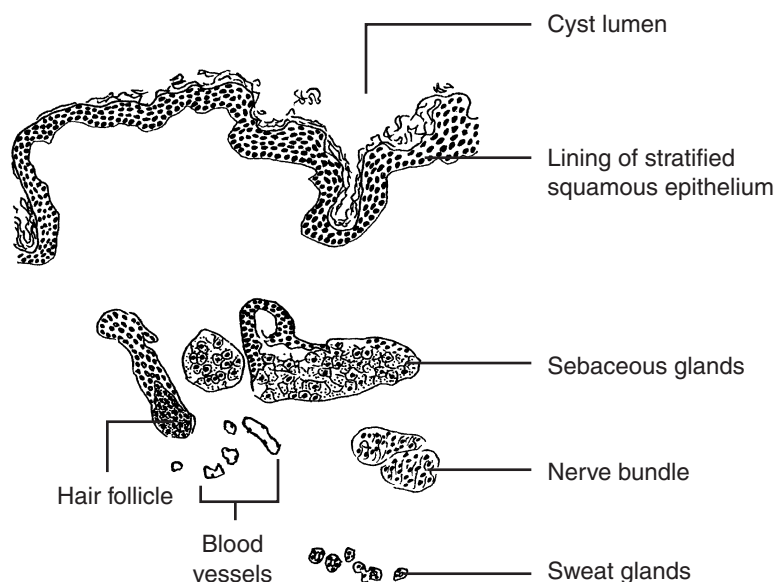
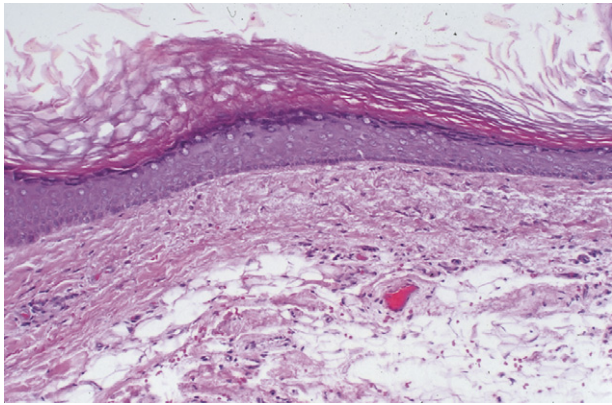


FIGURE 2-41

A, Dermoid cyst in this 18-year-old female is located between the mylohyoid muscle and present as a subcutaneous swelling below the chin. **B**, Cyst lumen is lined by an orthokeratinizing stratified squamous epithelium with hair follicle, sebaceous glands, and sweat glands in the capsule.



**FIGURE 2-42**

Epidermoid cyst. Microscopic appearance of cyst wall reveals a lumen lined by stratified squamous epithelium with a thickened layer of orthokeratin and a connective tissue capsule devoid of skin appendages.

CYSTS OF MUCOSAL EPITHELIUM

Surgical Ciliated Cyst of Maxilla

SURGICAL CILIATED CYST OF MAXILLA: *An intra-bony cyst located near the floor of the maxillary sinus lined by pseudostratified ciliated columnar epithelium, caused by implantation of normal mucus-secreting sinus epithelium during previous surgery.*

The surgical ciliated cyst of the maxilla is an iatrogenic cyst that develops as a result of surgery involving the maxillary sinus, usually a Caldwell-Luc operation. The cyst develops from maxillary sinus lining that becomes implanted in the maxillary bone at the site of surgical entry into the sinus. Although this cyst is rarely seen in the United States and Europe, it is not uncommon in Japan, where its occurrence has been attributed to the management of a higher incidence of maxillary sinusitis in that country.

CLINICAL FEATURES

This cyst occurs in middle age or older adults and is discovered during radiographic investigation of pain or tenderness in the maxilla. The patient's history usually discloses a previous surgery involving the maxillary sinus (Caldwell-Luc procedure) at the site of the cyst.

RADIOGRAPHIC FEATURES

The lesion presents as a well-circumscribed radiolucency in close proximity to, but separate from, the maxillary sinus.

HISTOPATHOLOGY

The cyst is lined by pseudostratified ciliated columnar epithelium exhibiting the features of maxillary sinus lining. The surrounding connective tissue may be normal or may exhibit some degree of chronic inflammation.

TREATMENT

This cyst is treated by conservative surgical enucleation and has no tendency to recur.

Heterotopic Oral Gastrointestinal Cyst

The heterotopic oral gastrointestinal cyst is a rare and unusual developmental entity that is most commonly found in the tongue or the floor of the mouth of infants or young children. Several theories have been proposed to explain the presence of gastrointestinal tract epithelium in the oral cavity. The theory of undifferentiated endodermal entrapment during the fourth or fifth week of embryonic development, followed by gastrointestinal differentiation, is a plausible explanation for the development of this cyst. This cyst is treated by surgical excision; recurrence is uncommon.

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3 *Infections of Teeth and Bone*

CHAPTER OUTLINE

DENTAL CARIES

Epidemiology
Clinical Types
Enamel Caries
Dentin Caries

PULPITIS

Reversible Pulpitis
Irreversible Pulpitis
Pulpal Necrosis
Common Diagnostic Techniques
History and Nature of Pain
Reaction to Thermal Changes
Reaction to Electrical Stimulation
Reaction to Tooth Percussion
Radiographic Examination
Visual Clinical Examination
Palpation of Surrounding Area
Histopathology of Pulpal Disease
Acute Pulpitis
Chronic Pulpitis
Chronic Hyperplastic Pulpitis

PERIAPICAL LESIONS

Chronic Apical Periodontitis
Periapical Granuloma
Periapical Cyst

ACUTE PERIAPICAL CONDITION

Periapical Abscess

OSTEOMYELITIS

Acute Osteomyelitis
Cellulitis
Chronic Osteomyelitis
Garré Osteomyelitis

ADDITIONAL KEY TERMS

Acute (rampant) caries
Cemental caries
Chronic caries
Dystrophic calcifications
Percussion test
Pit and fissure caries
Pulp polyp
Pulp stones
Pulpal abscess
Recurrent caries
Residual cyst
Sequestrum
Smooth surface caries



DENTAL CARIES

Dental caries is a multifaceted disease involving interplay among the teeth, the oral host factors of saliva and microflora, and the external factor of diet. The disease is a unique form of infection in which specific strains of bacteria accumulate on the enamel surface, where they elaborate acidic and proteolytic products that demineralize the surface and digest its organic matrix. Once penetration of the enamel has occurred, the disease progresses through the dentin to the pulp. If the process is not stopped, the tooth becomes destroyed. The clinician can intercept the process within the tooth by mechanically removing the infected tooth tissue and replacing it with an appropriate synthetic material that restores the tooth to normal form and function. Although dental caries is restricted to the hard tissue of the enamel, dentin, and cementum, if left untreated, the process will ultimately penetrate through the pulpal canal beyond the tooth into the adjacent soft tissue, where it will initiate a painful and destructive inflammatory reaction. In this location it may spread into the marrow spaces of the bone and possibly the soft tissues and muscles of the face and neck.

EPIDEMIOLOGY

Although dental caries is ubiquitous, its prevalence and severity differ among various populations throughout the world. The caries activity in a particular society or geographic area is closely correlated with the amount of sugar consumed per capita. In the more industrialized countries, where diets have traditionally had a high content of refined carbohydrates, the caries rate has been considerably higher than in less-developed countries. In recent years with the trend toward preventive measures such as fluoridated water, greater access to dental care and better oral hygiene in industrialized countries, and the concurrent rapid increase in caries activity in the less-developed societies, the large difference in caries rates has decreased. This latter phenomenon in the less developed countries is due to the recent increase in the consumption of sugar as a cheap source of body energy, the introduction of Western diets containing refined foods, the inability to maintain the necessary level of oral hygiene, and the unavailability of professional dental care.

In the Western world, susceptibility to dental caries differs significantly among age groups, individual teeth, and tooth surfaces. In the very young, when diets are high in sucrose and without adequate preventative practices, the pits and fissures of the first molars commonly become involved with caries within the first 3 years after eruption.

The second molars have the next highest susceptibility, followed by the second premolars. If the oral envi-

ronmental factors are extremely cariogenic, the smooth surfaces of the molars and premolars will be affected; first the interproximal surfaces become involved, followed by the buccal and lingual surfaces. Under extraordinary circumstances the smooth surfaces of anterior teeth also develop lesions. These surfaces are the most resistant, because they are relatively self-cleansing.

CLINICAL TYPES

Clinically, dental caries is classified as **pit and fissure**, **smooth surface**, **cemental**, and **recurrent** (Box 3-1). In addition, caries may be further classified as **acute (rampant)** or **chronic**.

Pit and fissure caries is the most common type and appear at an early age on the occlusal and buccal surfaces of the molars of the primary and secondary dentition (Figure 3-1). The occlusal surfaces of the premolars and the lingual surfaces of the maxillary incisors will also become less frequently involved. This form of caries is the most destructive, because it quickly goes deeply into the dentin, remains hidden as it undermines the enamel, and becomes clinically evident as pain caused by pulpal involvement or as a large cavity when a substantial portion of the tooth crumbles.

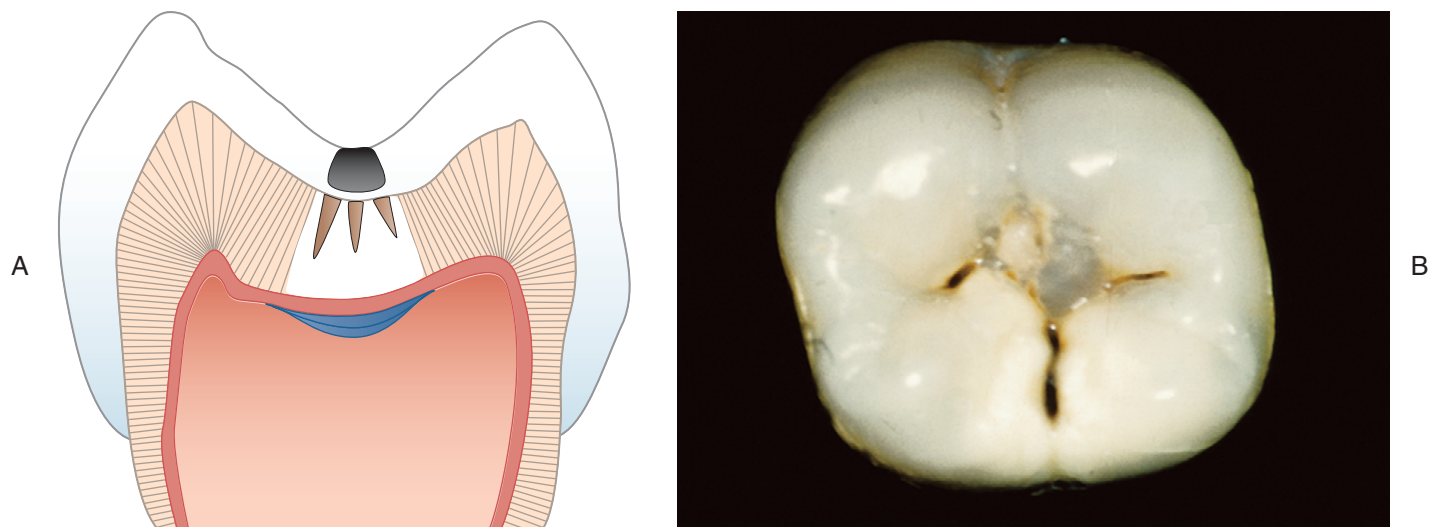
Smooth-surface caries is less common and essentially occurs on the interproximal (contact) areas of the teeth that are not self-cleansing (Figure 3-2). On occasion, the cervical regions of the buccal (Figure 3-3) and lingual surfaces of the teeth will become involved. Such occurrences are usually related to unusual circumstances.

When caries is present on the labial surfaces of the primary teeth of infants, it is nearly always caused by a habit of leaving the feeding bottle containing milk or juice in the infant's mouth when sleeping (Figure 3-4). In adults, smooth-surface cervical caries is usually the result of a major alteration in the quantity or quality of the saliva. Patients who have had radiation therapy for head and neck malignancies will sustain substantial irreversible damage to the major salivary glands, which results in severely altered saliva. Patients who develop autoimmune diseases that involve the major salivary glands and patients on medications that reduce saliva production as a side effect will be similarly affected.

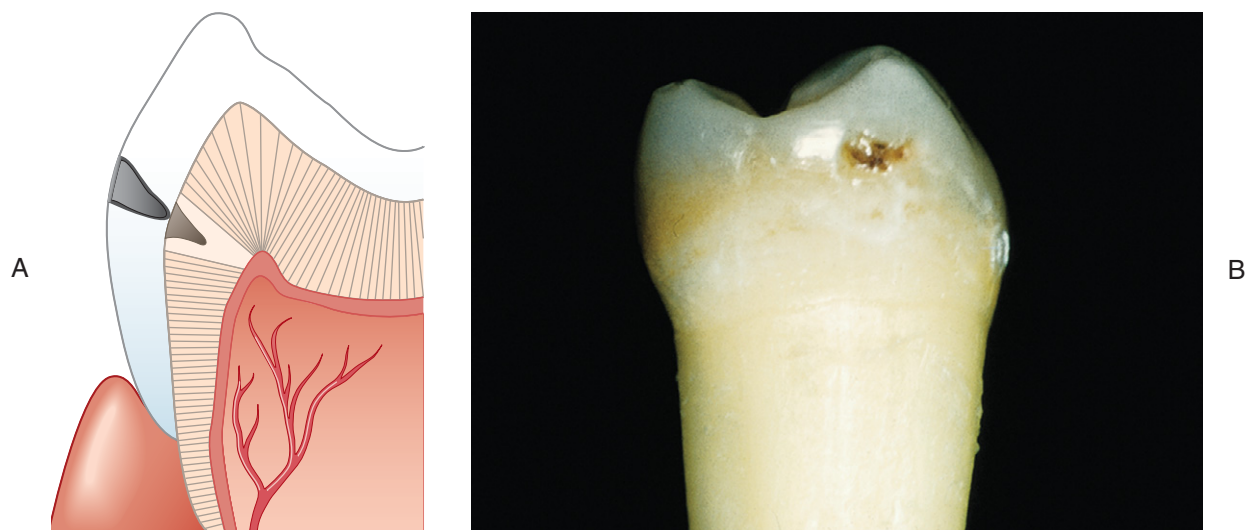
BOX 3-1

Clinical Classification of Dental Caries

- Pit and fissure
- Smooth surface
- Cemental
- Recurrent

**FIGURE 3-1**

Pit and fissure caries. **A**, The characteristic shape of lesions demonstrating a small triangle-shaped lesion in the fissure of the occlusal enamel (*gray-black*) that appears narrow at the surface but wider at the dentoenamel junction to provide an even greater involvement of dentin (*dark brown*). The pulp of the tooth reacts with the deposition of reparative dentin (*blue*). **B**, Clinical appearance of molar with fissure caries, exhibiting the black areas of disintegration at the base of the fissure and the demineralized and undermined white opaque areas surrounding the enamel.

**FIGURE 3-2**

Smooth-surface caries. **A**, The characteristic triangular shape of these lesions that corresponds to the orientation of the enamel rods and the dentinal tubules. **B**, Clinical appearance of early enamel caries on the smooth interproximal surface, exhibiting the central brown zone of disintegration.

Cemental (root) caries is nearly always exclusively found in the older population, particularly in those who have experienced substantial gingival recession. This form of caries is initiated and progresses differently than enamel and dentin caries, because root surfaces are

soft, thin, and subject to chemical erosion and the abrasive action incurred during toothbrushing. The combination of both acid- and enzyme-producing bacteria and the thin layer of dentin results in rapid progression of lesions into the pulp. This type of carious lesion presents

**FIGURE 3-3**

Smooth-surface caries. Clinical appearance of white "chalky" lesions of enamel demineralization (maxillary premolar and cuspid) and cavitation (lateral incisor) in a patient with rampant caries.

**FIGURE 3-4**

"Baby-bottle caries" on labial surfaces of the anterior primary teeth in a young patient.

**FIGURE 3-5**

Cemental (root) caries. **A**, Multiple carious lesions on the root surfaces of mandibular teeth in a patient with extensive gingival recession. **B**, Radiograph of a mandibular premolar with deep caries on the distal root surface in close proximity to the pulpal canal.

considerable difficulties to the clinician, because it is located in the soft surrounding cemental tissue in a region of the tooth where little tooth structure overlies the pulp (Figure 3-5).

Recurrent caries is the term applied to caries that arises around an existing restoration. Lesions usually arise as a result of an alteration in the integrity of a restoration that results in marginal "ditching" or leakage. These situations predispose the tooth to the accumulation of bacteria and food in an environment protected from the usual hygiene procedures. These carious lesions progress at variable rates, depending on the extent of sclerosis of the adjacent dentin and the patient's diet and oral hygiene habits.

Acute (rampant) caries and *chronic caries* are infrequently used terms to denote the rate that dental caries progresses in patients. Young patients are most susceptible to acute or rampant caries, because they have teeth with large pulpal chambers and wide and short dentinal tubules containing little or no sclerosis. In these patients this is often combined with a diet high in refined carbohydrates and less-than-adequate oral hygiene.

They are capable of simultaneously developing multiple rapidly advancing carious lesions that quickly destroy tooth structure, penetrate into the pulp, and elicit severe pain. Chronic caries is most common in older patients whose teeth have smaller pulpal chambers, usually with additional deposits of a denser and less

tubular dentin on the pulpal walls, referred to as *tertiary* or *secondary dentin*. Additionally they have dentinal tubules that have undergone significant degrees of sclerosis, which offers some degree of resistance to the progression of the carious process. These patients may experience pain, but it is seldom of the degree that younger patients with the acute form of caries experience.

ENAMEL CARIES

Smooth-surface enamel caries is most commonly located on the mesial and distal surfaces at the point of contact with the adjacent tooth (interproximal caries). The less common lesions on the buccal and lingual surfaces have a similar microscopic appearance. Because the enamel is composed primarily of inorganic salts, the process results in the production of a cavity because of demineralization. To achieve this end, a prior stage exists in which alteration occurs in the loss and redeposition of mineralizing salts that is caused by fluctuations in the pH in that particular location. In some situations if the pH can be stabilized in its normal range, the whole process may stop or even reverse, which is referred to as *arrested caries*. Arrested caries may also occur when an adjacent tooth is extracted (Figure 3-6) or when an undermined cusp fractures off, making the carious area self-cleansing. In some patients, a sudden and persistent improvement in oral hygiene habits can halt progression of early enamel lesions.

HISTOPATHOLOGY

Smooth-surface caries progress in a cone-shaped manner, being wider at the outer surface than at the deeper advancing margin. When a thin ground section of an early

lesion (before cavitation) is viewed with light microscopy, four zones can be identified (Figure 3-7): (1) *translucent zone*, the advancing front of initial demineralization; (2) *dark zone*, where the previously liberated salts are redeposited; (3) *body of lesion*, containing the region

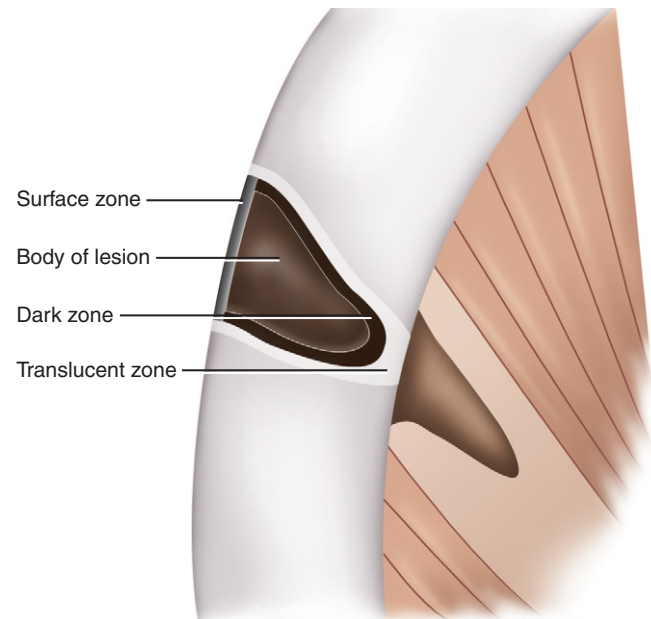


FIGURE 3-7
Enamel caries. Microscopic zones of enamel caries.

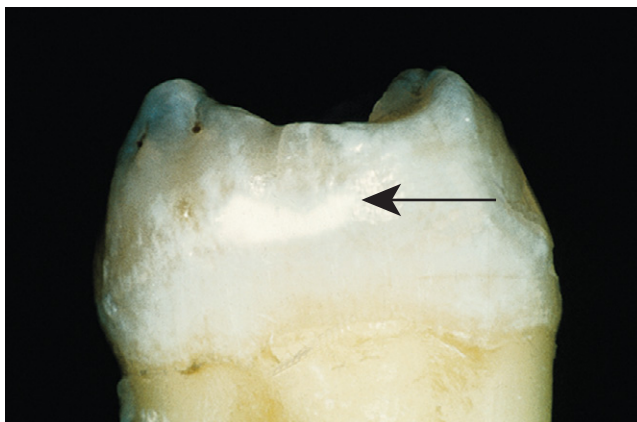


FIGURE 3-6
Smooth-surface enamel caries. Example of a superficial lesion (arrow) capable of being arrested from further progression if oral hygiene is improved.



FIGURE 3-8
Enamel caries. Advanced interproximal smooth-surface lesion with cavitation.

of maximal demineralization; and (4) *surface zone*, remaining relatively unaffected until it is sufficiently undermined to collapse, resulting in cavitation (Figure 3-8).

In their early stages, pit and fissure enamel caries have histologic zones similar to smooth-surface carious lesions. The shape of the lesion differs because of the different angulations of the enamel rods. These lesions will be wider in the deeper portion and will have a wider area of involvement of the dentinal tubules at the dentinoenamel junction than at the surface. This, and the fact that the enamel is much thinner at the base of the pit or fissure, results in the lesions progressing at a much faster rate than the smooth-surface type.

DENTIN CARIES

In general, dentin caries progresses at a much faster rate than enamel caries. It is more porous, because it contains dentinal tubules and is less densely mineralized. This stage of caries progression requires a different mixture of bacterial colonies than is necessary for enamel caries. For caries to progress in dentin, bacterial strains capable of producing large amounts of proteolytic and hydrolytic enzymes are needed, rather than the acid-producing types of enamel caries. In the teeth of younger patients the dentinal tubules are less densely mineralized, shorter in length, and wider in diameter, allowing for ease of penetration and progression of the invading microorganisms. In older patients, deposits of calcifying salts usually narrow the dentinal tubules, making the teeth less porous. In addition, the dentin will be thicker because of the production of additional normal and abnormal secondary dentin on the pulpal walls. Because of these differences,

dental caries in younger patients often quickly involves the pulpal tissue, which produces an acute inflammatory reaction and intense pain. However, in older patients it has a slower course with intermittent mild pain.

HISTOPATHOLOGY

A nondecalcified cross section of a tooth with an advanced carious lesion of the dentin that has not reached the pulp will show five microscopic zones that reveal the stages of dentinal caries that eventuates in a cavity (Figures 3-9, 3-10, and 3-11).

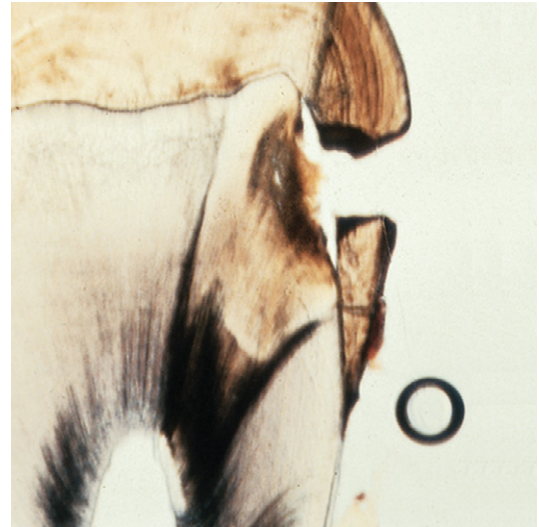


FIGURE 3-10

Dentin caries. Ground section of an advanced carious lesion of interproximal smooth-surface origin.

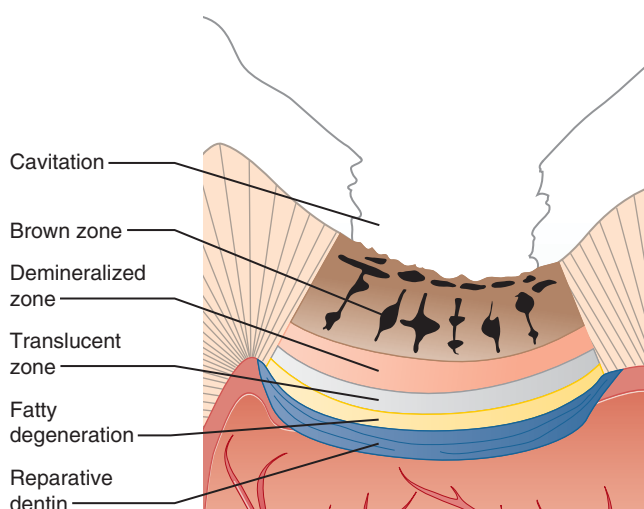


FIGURE 3-9

Dentin caries. Microscopic zones of an advanced carious lesion in dentin.

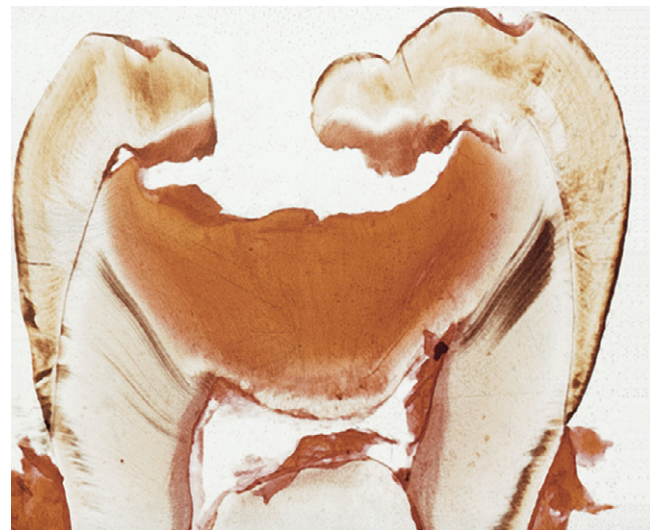
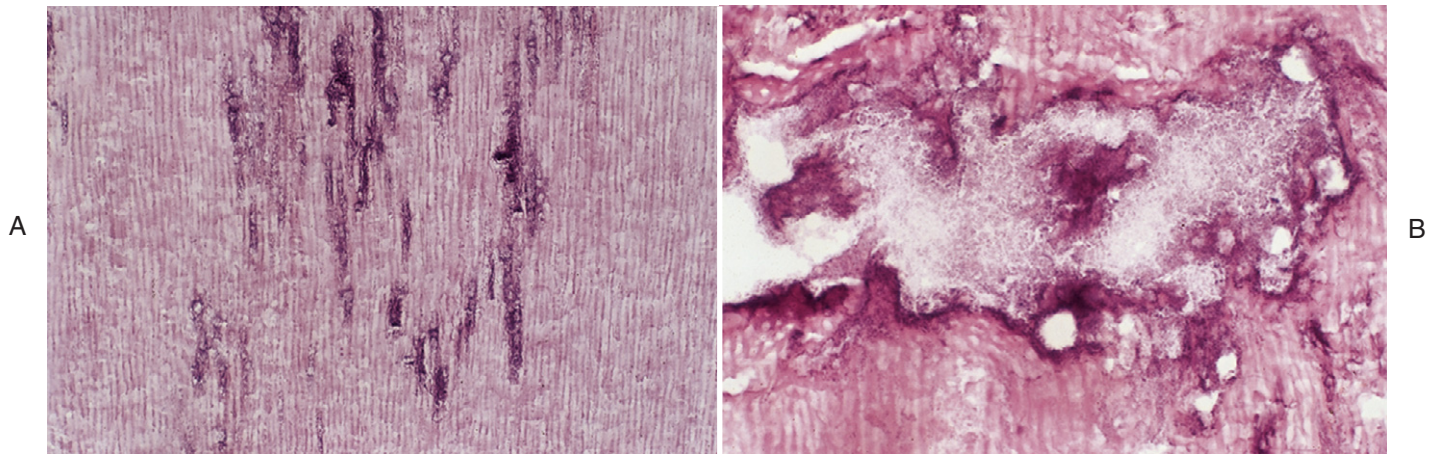


FIGURE 3-11

Dentin caries. Ground section of an advanced carious lesion of fissure origin.

**FIGURE 3-12**

Dentin caries. Microscopic appearance of dentin, exhibiting bacteria in the dentin tubules (A) and a large area of liquefaction of dentin caused by the horizontal fusion of the focal accumulations of bacteria within individual tubules ("transverse clefts") (B).

The deepest zone, **Zone 1, fatty degeneration**, reflects the earliest changes of caries infection where bacterial enzymes have advanced ahead of the bacteria in the dentinal tubules, causing a breakdown of the cell membranes of the organic component of the dentin-liberating lipid. **Zone 2, translucent zone**, is a band of hypermineralized dentin in which the dentinal tubules are sclerotic because of the redeposition of calcifying salts released from the demineralized zone. **Zone 3, demineralization**, is composed of dentin that is softer than normal because of the initial action of the bacterial enzymes. **Zone 4, brown discoloration**, is due to a reduction in the mineral content and the presence of distended dentinal tubules packed with bacteria. This zone is usually soft enough to be removed with a hand instrument. **Zone 5, cavitation**, differs from the previous zone, because no mineralization is present and the organic component is partially dissolved by the bacteria. This zone is the clinically observed base of a large cavity. It also has a brown coloration and easily peels away in layers along the incremental lines of growth. In Zone 5 the tubules will contain focal, dense accumulations of bacteria that form liquefaction foci, referred to as *beading* (Figure 3-12, A). These foci fuse horizontally, producing *transverse clefts* (Figure 3-12, B). These microscopic features are apparent to the clinician because of the ease with which the layers of dark brown, soft dentin present at the base of the cavity can be peeled away with a spoon excavator.

PULPITIS

PULPITIS: An inflammation of the pulpal tissue that may be acute or chronic, with or without symptoms, and reversible or irreversible.

The single most frequent diagnostic problem that clinicians confront in their daily practice is to determine the extent of the pulpal disease that has taken place within a symptomatic tooth. To make this decision, it is necessary for the clinician to be able to make an evaluation of the damage to the pulpal tissue that can be neither seen nor touched. An indirect assessment is required based on a combination of clinical tests and knowledge of the biologic and pathologic processes that occur within pulp tissue.

The decision to be made is one of the following: (1) to restore the defective tooth structure conservatively, (2) to remove the diseased pulpal tissue, or (3) to remove the entire tooth. In making the decision the clinician is really deciding whether the disease process taking place within the pulp is a **reversible** (Figure 3-13) or an **irreversible pulpitis**.

Although pulpitis has a large number of possible causes (Box 3-2), the primary one is dental caries. Because dental caries destroys tooth structure, the extent to which the tooth is able to be restored plays a large part in the decision whether to treat the pulpitis without removing the pulpal tissue, to remove the diseased pulp and restore the tooth, or to remove the tooth.

Pulpitis is the name given to any inflammation of the pulp regardless of the presence of an infectious agent. Because the pulp is contained within a solid unyielding chamber with a limited blood supply through the apical foramen and no collateral support, the inflammatory process that is so beneficial in the healing process in other parts of the body often becomes a mechanism of destruction in this confined location. Inflammation is by nature an expansile process consisting of dilation of blood vessels, leakage of fluids from blood vessels into

the surrounding connective tissue, and migration of cells into the immediate area. In the pulpal chamber if the inflammatory process continues for an extended period or is particularly intense, it can produce sharp and prolonged pain because of the internal pressure and strangulation of the blood supply. Without intervention, an acute form of pulpitis rapidly progresses to pulpal necrosis.

BOX 3-2

Causes of Pulpitis

BACTERIAL

Caries
Cracks in crown
Periodontal pockets
Malformed teeth

TRAUMATIC

Crown fractures
Root fractures
Partial avulsion
Bruxism
Abrasion

IATROGENIC

Heat generation
Depth of preparation
Dehydration of tubules
Pulp exposure
Volatile/toxic disinfectants
Filling materials

REVERSIBLE PULPITIS

The diagnosis of reversible pulpitis implies that the pulp is capable of a full recovery if the irritating factors subside or are removed. The symptoms reflect an irritated pulp tissue that reacts with the mildest and earliest forms of the inflammatory response, consisting of vasodilation, some transudation, a slight infiltrate of lymphocytes, and disruption of the odontoblastic layer (Figure 3-14). The diagnosis is based on the ability of the clinician to properly assess the patient's history and clinical signs and symptoms. To differentiate between reversible and irreversible pulpitis, the following must be assessed:

1. Whether the pain is spontaneous or brought on by thermal changes
2. The duration of each episode of pain
3. The nature of the pain as described by the patient

The pain of reversible pulpitis is sharp and intense and responds to a sudden change in temperature. The pain generally remains for 5 to 10 minutes and seldom lasts longer than 20 minutes. The tooth remains without symptoms until it is stimulated again. Changes in the position of the body, such as lying down, do not generally affect the nature or the duration of the pain. The treatment of reversible pulpitis consists of protecting the pulp from further thermal stimulation and placing sedative dressings in the base of the carious defect for several weeks.

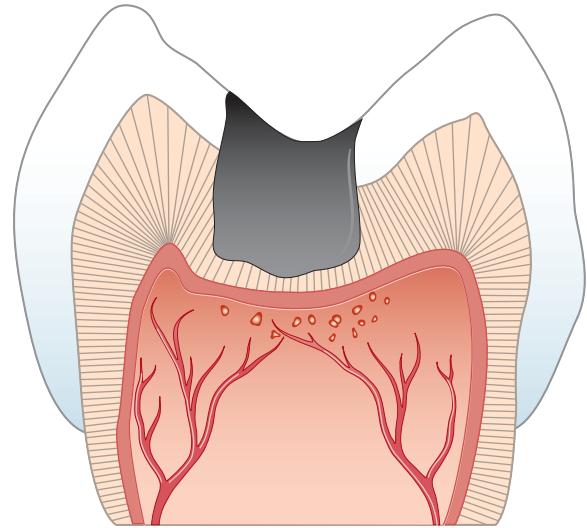


FIGURE 3-13

Reversible pulpitis. Mild transient pulpal inflammation that occurs immediately after the placement of a deep restoration.

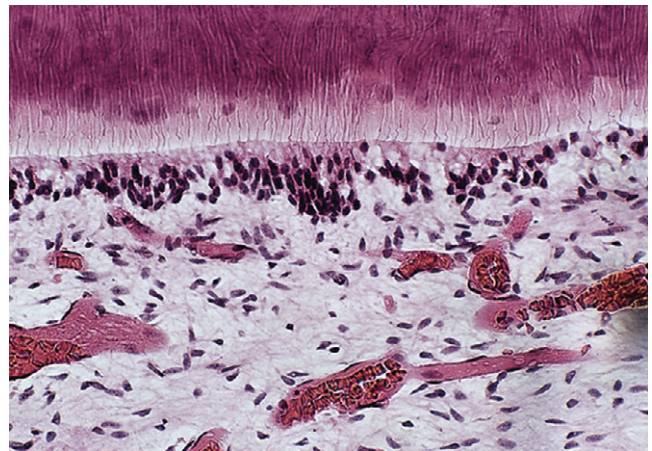


FIGURE 3-14

Reversible pulpitis. Microscopic features of dilated blood vessels and the slight disruption of the odontoblastic layer.

IRREVERSIBLE PULPITIS

The diagnosis of irreversible pulpitis is made when it is determined that the pulp will most likely not recover, regardless of the attempts to treat it. The pulpal tissue will exhibit a wide spectrum of acute and chronic inflammatory changes (Figure 3-15). For the patient to obtain permanent relief at this stage, the remaining pulp must be removed or the tooth must be extracted. The diagnosis is made based on the same type of clinical information used to diagnose reversible pulpitis.

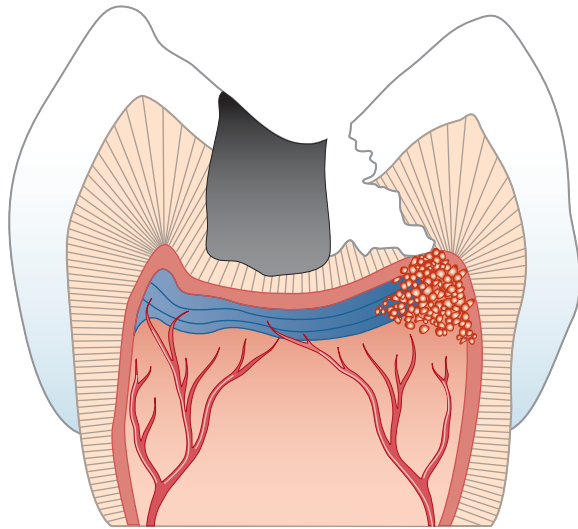


FIGURE 3-15
Irreversible pulpitis. A focal area of acute inflammation (pulpal abscess) in a tooth with advanced recurrent caries.

BOX 3-3

Comparison of Pain Symptoms in Reversible and Irreversible Pulpitis

REVERSIBLE	IRREVERSIBLE
Elicited	Spontaneous
Sharp	Dull
<20 minutes' duration	>20 minutes' duration
Unaffected by body position	Affected by body position
Easily localized	Often difficult to localize

The pain of an irreversible pulpitis can be of variable intensity, but it is usually less intense than that of reversible pulpitis. The main feature of irreversible pulpitis is that pain is spontaneously initiated, not the result of a sudden temperature changes, and it lasts for a prolonged period, usually longer than 20 minutes. The pain may be initiated or accentuated when the patient reclines. Although the pain from reversible pulpitis is easily localized to a particular tooth, the pain from an irreversible pulpitis may be referred to another nearby location, such as the lateral aspect of the face or to other teeth in the arch (Box 3-3).

PULPAL NECROSIS

Pulpal necrosis is the term applied to pulp tissue that is no longer living. If this is the result of a sudden traumatic event, such as a blow to the tooth in which the



FIGURE 3-16
Pulpal necrosis. Darkened central incisor caused by penetration of the tissue remnants of nonvital pulp into the dentin tubules. The small nodule on the gingiva above the tooth (parulis) is the surface opening of a drainage tract from a periapical abscess.

blood supply has been severed, the patient will often have no symptoms for a time. In other cases, pulpal necrosis occurs slowly over time, as occurs during the course of an untreated irreversible pulpitis. In this latter case the patient may gradually lose the acute and chronic symptoms, because the nerve fibers in the pulp degenerate from the overwhelming inflammation. In either situation the asymptomatic state is usually temporary, because the pulpal tissue soon undergoes autolysis, becoming a source of irritation to the periodontal membrane tissue adjacent to the apical foramen.

In pulpal necrosis the pulpal tissue may be infected with bacteria. Infected pulpal necrosis is usually the result of dental decay, in which case the infection can quickly extend into the apical areas of the tooth and the surrounding bone. These occurrences produce a great deal of pain and other systemic reactions. Noninfected (aseptic) pulpal necrosis usually occurs after a traumatic incident and may not produce symptoms for many months. The first sign of noninfected pulpal necrosis may be a change in the coloration of the tooth (Figure 3-16). This is the result of the decomposing tissue debris and breakdown products of the red blood cells entering the open ends of the empty dentinal tubules and becoming distributed throughout the dentin. This process alters the translucency of the tooth. After the tooth has become nonvital, it loses its ability to rehydrate the dentin, making it more brittle and subject to cracks and fractures.

The presence of the inflammatory response in the apical periodontal membrane can produce extensive pain because of its location in a confined area between the alveolar bone and root surface. Until the surrounding bone undergoes resorption, allowing the accumulated edema and exudate to escape into the marrow

spaces, the pressure from the exudate may force the tooth to extrude from the socket causing premature contact with opposing teeth. This tooth will be sensitive to even the smallest amount of pressure, including contact when chewing food.

A diagnostic tool used to determine if a tooth has undergone pulpal necrosis consists of gently tapping on several teeth in the area with a blunt instrument. A tooth that has undergone pulpal necrosis will be identified, because the pressure from the tapping will produce intense pain. This is referred to as the *percussion test*.

COMMON DIAGNOSTIC TECHNIQUES

The diagnostic procedures that are commonly used to assess the status of a symptomatic tooth and pulp are as follows:

1. History and nature of pain
2. Reaction to thermal changes
3. Reaction to mild electric stimulation
4. Reaction to tooth percussion
5. Radiographic examination
6. Visual clinical examination
7. Palpation of surrounding area

History and Nature of Pain

The history and nature of the pain relate to the circumstances of its occurrences, such as duration and the type of sensation experienced by the patient. The pain of reversible pulpitis is sharp and intense, whereas the pain of irreversible pulpitis is often described as dull, nagging, and frequently vague in its location.

Reaction to Thermal Changes

The test for a reaction to thermal changes is conducted in the dental office by placing a cold or very warm object on the tooth. If the patient has reversible pulpitis, an immediate, sharp pain that last for up to 20 minutes will occur. If the patient has irreversible pulpitis, the pain may be less sharp or dull but may last for a much longer time.

Reaction to Electrical Stimulation

The test for reaction to electrical stimulation is conducted with low-voltage direct current. It evaluates the degree of excitability of the nerves in the inflamed pulp. In reversible pulpitis the nerves will be easily excited and will thus respond at a lower-than-normal voltage level. In irreversible pulpitis the nerve tissue within the pulp is more severely damaged, and a higher level of voltage is required before the patient responds. This diagnostic test is often variable. It is most useful when no

reaction takes place, even at the highest voltage level; this lack of reaction suggests that no live pulpal tissue remains.

Reaction to Tooth Percussion

A positive reaction to percussion indicates that inflammation exists in the apical periodontal tissue of a particular tooth. At this point a large part of the pulpal tissue, if not all of it, is nonvital. This is particularly useful when the pain is vague and the offending tooth is not immediately apparent, as occurs with long-standing irreversible pulpitis.

Radiographic Examination

A radiograph is of little use in evaluating the extent of changes within the pulpal chambers. It can be useful in determining if the irreversible inflammatory response has reached the periapical tissue and has been present in that location for a sufficient period of time to cause an increase in the width of the apical periodontal space. The presence of radiolucency at the apex of a tooth is of great help in determining the cause of vague pain in a quadrant of the mandible or maxilla.

Visual Clinical Examination

A visual clinical examination may reveal an expansion of the cortical plates of the alveolar bones. This is helpful if the periapical inflammation has penetrated into the surrounding bone and is attempting to drain to the surface. Sometimes a small, raised, reddish papule or nodule (parulis) occurs over the apex of the tooth that represents the stoma (opening) of a draining sinus tract of a periapical abscess.

Palpation of Surrounding Area

Palpation of the periapical area resulting in pain to the patient signifies that the inflammation has reached the tissue surrounding the apex of the tooth. This is an indication that the pulp is necrotic and the pulpal chambers need to be filled to prevent further spreading of the inflammation to the surrounding bone.

HISTOPATHOLOGY OF PULPAL DISEASE

Correlation of the patient's clinical signs and symptoms with the degree of pulpal histopathologic changes has been difficult and inaccurate. Attempts to assess whether a specific instance of irreversible pulpitis is actually an acute partial or total pulpitis, chronic partial or total pulpitis, fibrotic pulp, or any other severe inflammatory change should not be undertaken if evaluation is only

based on an analysis of the clinical signs and symptoms. A true evaluation of the actual degree of inflammatory pulpal changes can only be made if the tissue is actually removed and microscopically examined.

Because actually sampling the pulpal tissue quickly leads to its demise, this is not possible. The decision whether to remove the entire pulpal tissue must be based on the clinical information available. Extirpation of the pulp for examination (as a means of relieving pain or for other reasons) results in a devitalized tooth that requires the empty chamber to be filled with a synthetic material to prevent it from becoming a source of inflammation and infection to the adjacent periapical area.

Although no direct correlation exists between the clinical and histologic disease states of the pulp, a spectrum of histologic changes takes place between a normal and a necrotic pulp. Some of the histopathologic stages fluctuate for a time (e.g., acute-chronic-acute), whereas others are part of a one-way chronic progressive course that ends in fibrosis with focal or diffuse calcification or in pulpal necrosis.

Acute Pulpitis

The histopathologic features of an acute pulpitis are similar to those of an abscess in other parts of the body. Acute pulpitis may be confined to one horn of the coronal pulp (*focal acute pulpitis*) (Figure 3-17) or involve the whole pulp (*total acute pulpitis*). The condition is usually the result of rapid bacterial invasion of large-diameter (nonsclerosed) dentinal tubules and is most commonly found in the teeth of children and adolescents. For a pulpitis to remain acute, there must be no possibility of

drainage of the exudate. Instead the exudate remains within the enclosed chamber, builds pressure, and quickly extends to all parts of the healthy pulp.

An acute pulpitis can arise when the pulp becomes suddenly overheated to the extent that the blood vessels rupture, causing focal areas of hemorrhage. This may occur during crown preparation, when inadequate cooling does not accompany the high-speed removal of the tooth structure (Figure 3-18).

A **pulpal abscess** is similar but not identical to an abscess in any other part of the body. The core is composed of a purulent exudate consisting of polymorphonuclear leukocytes against a background of fibrin, necrotic tissue debris, and extravasated red blood cells. A zone of granulation tissue consisting of newly formed capillary blood vessels, plump fibroblasts, plasma cells, and lymphocytes surrounds this core. Because the pulpal tissue is small and the process in this location is usually rapid, no outer surrounding fibrous connective capsule exists, as occurs in other body locations. The liberated autolytic enzymes that result from tissue destruction and the exotoxins of the invading bacteria quickly spread to all parts of the remaining healthy pulp and eventually through the apical foramen into the adjacent periodontal membrane. Because of the intenseness of the irritant in the form of virulent bacteria and the lack of drainage, purulent exudate penetrates the cortical bone surrounding the apical periodontal membrane and invades the marrow spaces of the medullary bone. At this point the condition represents a form of focal acute suppurative osteomyelitis. If drainage occurs at or before this stage, the histopathologic features would quickly revert to those of the chronic form of pulpitis.

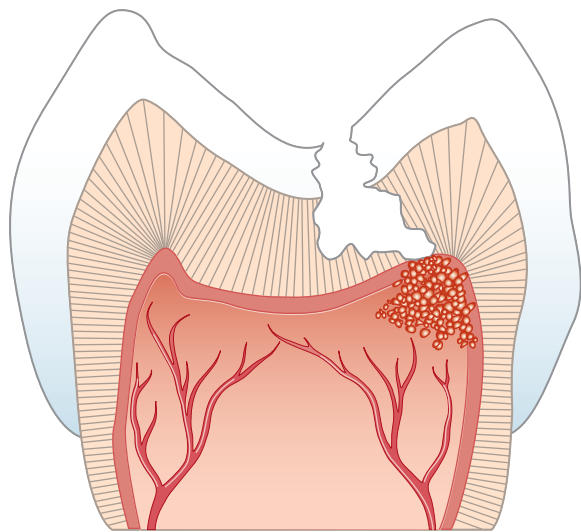


FIGURE 3-17
Acute pulpitis. An abscess of the pulpal horn common in teeth of young patients.

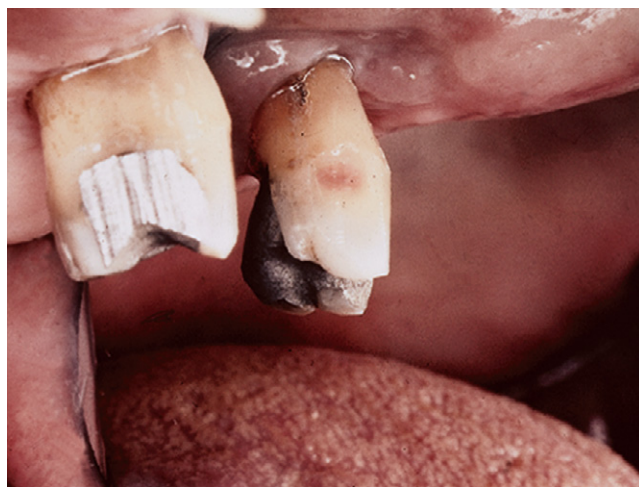


FIGURE 3-18
Acute pulpitis. Tooth exhibiting a focal area of intrapulpal hemorrhage and acute pulpitis resulting from overheating during crown preparation.

Chronic Pulpitis

The histologic features of a **chronic pulpitis** are similar to those of a chronic focal fibrosis in other parts of the body that is caused by a low-grade irritant (Figure 3-19). Chronic pulpitis occurs when there is little or no pene-

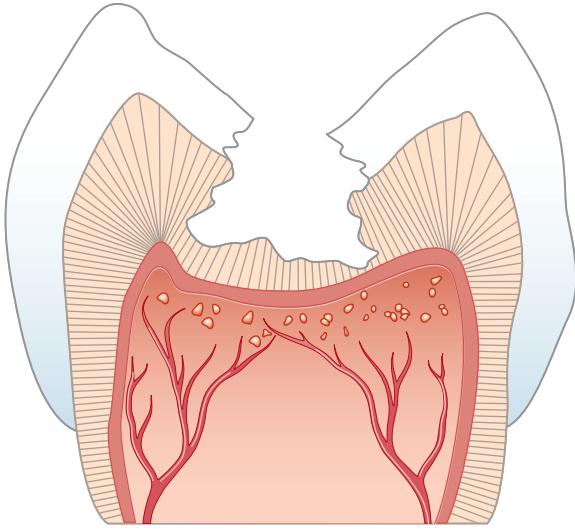


FIGURE 3-19

Chronic pulpitis. A large carious lesion in an older tooth in which the pulpal tissue contains a diffuse infiltrate of inflammatory cells.

tration into the pulp by large numbers of the virulent types of bacteria. This is often the situation in older teeth, because most of these teeth have had previous restorations or a slowly progressive form of caries. This form of caries allows the dentinal tubules to narrow (sclerosis) and the pulpal dentin to deposit tertiary (reparative) dentin at its interface with the pulpal soft tissue. This relatively nontubular form of dentin or bone, in addition to the sclerosed dentinal tubules, acts as a barrier to slow the progression of bacteria and their exotoxins, allowing the pulp to develop its own immune response.

When viewed microscopically, chronic pulpitis reveals the presence of loose, delicate connective tissue with bundles of dense collagen and a severe reduction in both the size and number of the vascular structures and peripheral nerves. A diffuse infiltrate of lymphocytes and plasma cells exists throughout the pulp. This stage of pulpal disease is referred to as **pulpal fibrosis**. If this stage persists for a time, focal and diffuse calcifications often occur. The calcifications may be in the form of **pulp stones** (spherical calcifications) (Figure 3-20, A) or **dystrophic calcifications** (linear calcifications) (Figure 3-20, B) and may be present in both the coronal and root pulpal tissues.

Eventually, prolonged chronic pulpitis leads to pulpal necrosis. The periapical lesion associated with chronic pulpitis is indolent and asymptomatic, and it is composed of a circumscribed nodule of fibrous tissue with a mild infiltrate of lymphocytes and plasma cells. This lesion is referred to as a *periapical granuloma*.

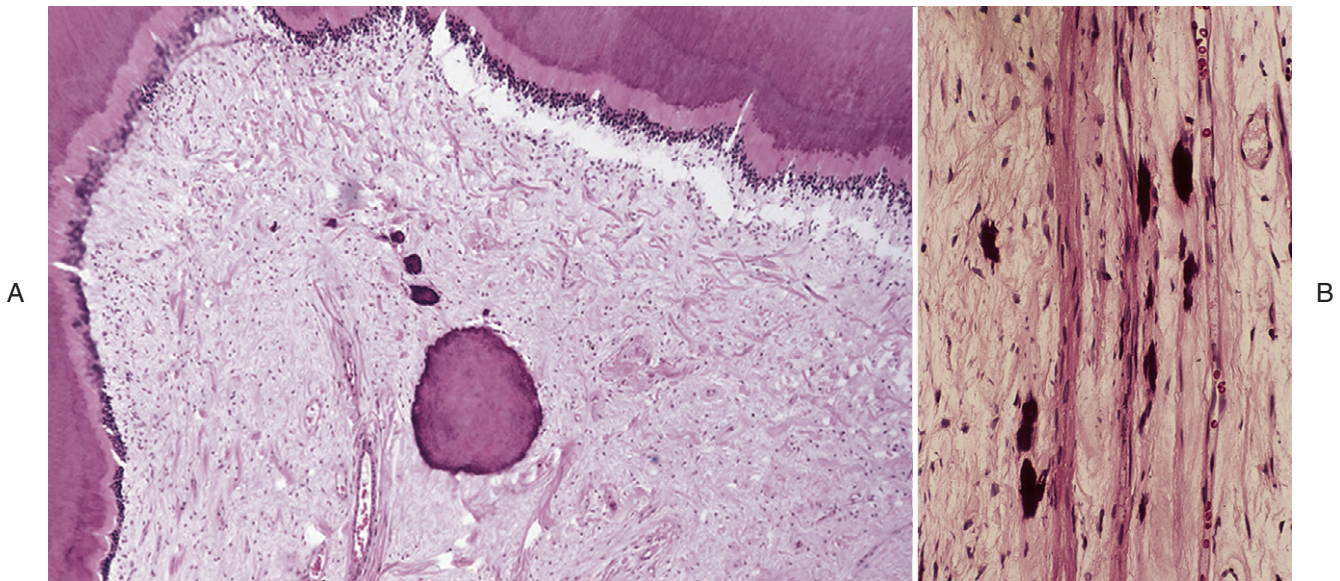


FIGURE 3-20

Chronic pulpitis. Microscopic appearance of pulp with spheric calcifications (pulp stones) (A) and linear (dystrophic) calcifications (B).

Chronic Hyperplastic Pulpitis

Chronic hyperplastic pulpitis is a rare condition that is primarily confined to the molars of children. It is the result of rampant acute caries in young teeth that quickly reaches the pulp before it becomes completely necrotic. In this rapid form of caries, the crown will sometimes disintegrate before the young, well-nourished pulp succumbs to infection, resulting in an open pul-

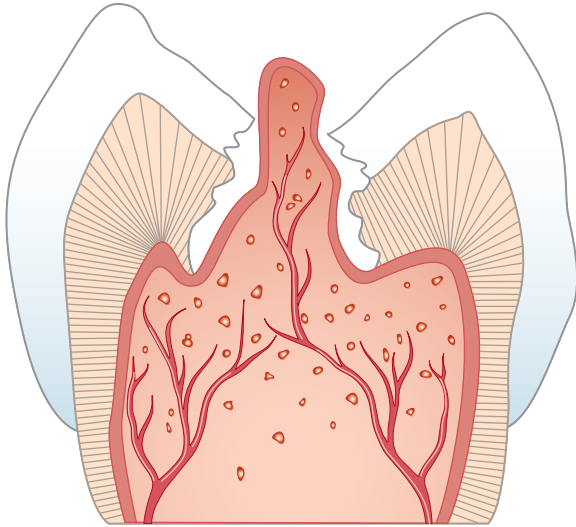


FIGURE 3-21
Hyperplastic pulpitis. A molar in a young patient with a chronically inflamed pulp that has proliferated through the open carious defect projecting into the oral cavity.

pit. In patients of this young age the apical foramen is often still widely open, allowing for an ample blood supply that is able to sustain the injured pulp. The combination of an open chronic pulpitis, an ample blood supply, and the increased regenerative capacity of young pulpal tissue appear, in some instances, to stimulate the pulpal tissue to proliferate or to produce granulation tissue (Figure 3-21). Often this hyperplastic nodule will have a surface layer of stratified squamous epithelium. In this unusual series of events the pulpal tissue may undergo excessive overgrowth (hyperplasia) and project out of the crown of the tooth (Figure 3-22). The exposed tissue and the pulp remaining within the tooth eventually become fibrotic and produce a firm nodule. Because this lesion clinically projects from the pulpal chamber, it is commonly referred to as a *pulp polyp*.

Clinically, if a pulp polyp is not covered with epithelium or becomes ulcerated, it will appear reddish; otherwise, it has the same color as the rest of the oral tissue. Under normal circumstances these lesions produce no symptoms because they are said to be deficient in nerve fibers. If one of these polyps is found to be symptomatic, it is most likely not of pulpal origin but is instead an extension of the adjacent gingiva that is overlaying the disintegrated tooth crown.

The usual treatment of a tooth with a pulp polyp is extraction. If the molar is in the deciduous dentition, sometimes it is not extracted to maintain arch space. It should be remembered that the polyp cannot be effectively cleaned and that the remaining tooth structure will continue to decay, producing a chronic septic condition that can pose a health risk to the patient.



FIGURE 3-22
Hyperplastic pulpitis. **A**, Clinical appearance of pulp polyp in a grossly carious right mandibular first molar. **B**, Microscopic appearance of grossly carious tooth and fibrotic pulp polyp with a stratified squamous epithelium on the surface.

PERIAPICAL LESIONS

The nature and behavior of lesions that form at the apex of the tooth are a reflection of the conditions that lead to the destruction of the pulp of the associated tooth. The four major factors follow:

1. Presence of an open or closed pulpitis
2. Virulence of the involved microorganisms
3. Extent of sclerosis of the dentinal tubules
4. Competency of the host immune response

When the factors are optimal, such as the presence of an open chronic pulpitis, bacteria of low virulence, an older tooth with sclerotic dentinal tubules, and a healthy patient, the changes at the apex of the tooth are mild and chronic. Multiple optimal factors are sometimes associated with little or no activation of the inflammatory response; instead they act as stimulants to the fibroblastic and osteoblastic cells and scar tissue and dense bone produced in the area. When conditions are mostly adverse, such as the presence of a closed acute pulpitis, large numbers of highly virulent bacteria, and open dentinal tubules of young teeth, the inflammation at the apex of the tooth will rapidly intensify and large amounts of bacterial toxins and autolytic enzymes will be produced and disseminated. Under these circumstances rapid destruction of the periapical tissue and surrounding bone takes place; the process quickly extends into the adjacent marrow spaces (Figure 3-23).

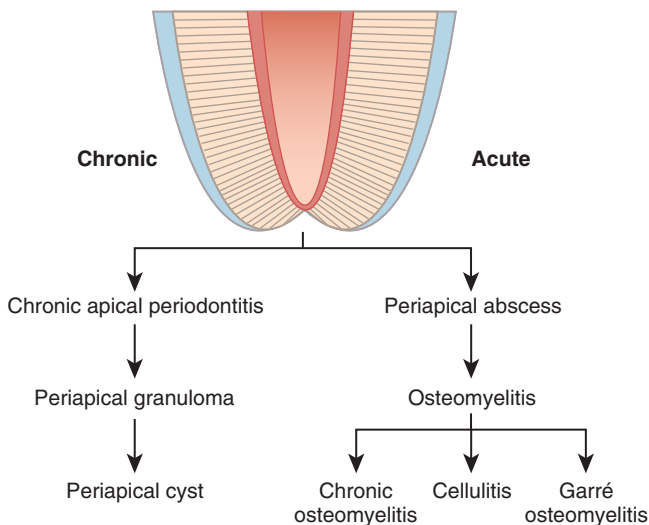


FIGURE 3-23

Periapical infections. Chronic and acute pathways that untreated infections and their accompanying clinical lesions may take, depending on the type of the preceding pulpitis, virulence of the bacteria, and the presence or absence of drainage.

CHRONIC APICAL PERIODONTITIS

The term *chronic apical periodontitis* is used to denote the earliest radiographic evidence of extension of the inflammatory process from the pulpal chamber into the adjacent periodontal membrane around the apical foramen. Although the outline of the apical alveolar bone is still visible on a radiograph, the periodontal membrane in this region will appear to be widened. Clinically the tooth may still exhibit some faint evidence of vitality when it is electrically stimulated, and it will usually have a positive reaction to a percussion test. The histopathologic findings are variable and will reflect the type of inflammation that existed in the pulp. This condition is merely a transitory phase between pulpitis and the more distinct forms of periapical lesions.

PERIAPICAL GRANULOMA

A *periapical granuloma* occurs when the contributing factors are optimal, such as when a pulpitis progresses into a periapical lesion. This is by far the most common lesion that occurs after pulpal necrosis. It is usually painless, progresses slowly, and seldom becomes very large. While a periapical granuloma is present, conditions can suddenly change. An open pulpal chamber may become blocked with food or a wooden toothpick, inhibiting drainage. When drainage of the exudate is inhibited, a periapical granuloma can be transformed into an acute periapical abscess. The most common change that occurs in a long-standing periapical granuloma is its gradual transformation into a periapical cyst. If the pulpal canal containing the necrotic tissue is not treated, a periapical cyst will gradually occur over the next several months to years.

RADIOGRAPHIC FEATURES

The radiographic appearance of periapical granuloma occurs as an oval or rounded radiolucency with a well-demarcated outline located at the apex of the tooth (Figure 3-24). Rarely the radiolucency will be located away from the apex and centered on the opening of a lateral canal. A periapical granuloma that periodically undergoes acute exacerbations will have a less distinct line of demarcation between the bone and the granulomatous tissue than a static, quiescent lesion. Frequent findings associated with a long-standing periapical granuloma are hypercementosis of the apical third of the root and resorption resulting in blunting of the root tip.

HISTOPATHOLOGY

A periapical granuloma is composed of an outer capsule of dense fibrous tissue and a central zone of granulation tissue (Figure 3-25). The central zone will often contain macrophages with a *foamy* cytoplasm caused by

phagocytized cholesterol. Some cholesterol crystals may be present, surrounded by multinucleated giant cells. Throughout, the soft tissue will be a diffuse infiltrate of lymphocytes and plasma cells. A frequent finding is the presence of irregular islands and strands of epithelium, a result of prolonged, mild stimulation of the *rests of Malassez*. These rests are the remnants of the

Hertwig root sheath, the epithelial membrane that determines the shape of the roots of developing teeth.

TREATMENT

The treatment of a periapical granuloma depends on the condition of the tooth as a whole. If the tooth is restorable, the root canal can be filled. If the root canal cannot be filled and the apical area is in a location accessible for surgery, an apicoectomy may be performed to remove the granuloma; otherwise, the tooth is extracted and the periapical granuloma is curetted through the tooth socket. Failure to resolve or remove a periapical granuloma commonly results in the development of a periapical cyst.

PERIAPICAL CYST

A periapical cyst is a common development of long-standing, untreated periapical granuloma. The cyst's epithelial lining is derived from the rests of Malassez, the epithelial islands remaining after root formation during odontogenesis and normally present in the apical periodontal membrane. The rests are stimulated to proliferate by the low-grade inflammation of the preceding periapical granuloma (Figure 3-26). The periapical cyst is by far the most common of the cysts of the jaws. Because its development is the result of sequential inflammation of the tooth pulp and the adjacent surrounding apical tissue, the cyst may become inflamed

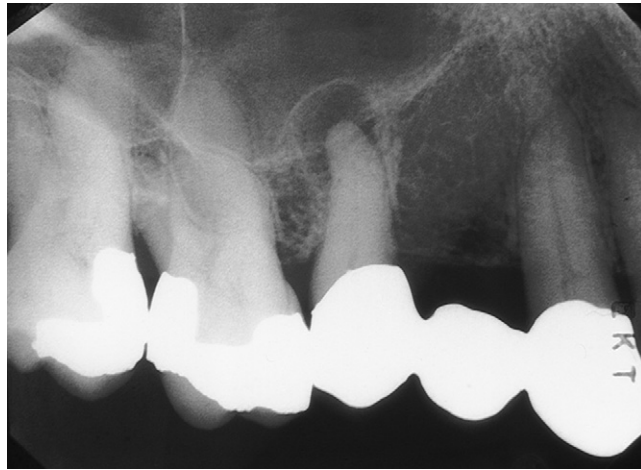


FIGURE 3-24
Periapical granuloma. Radiograph of a periapical granuloma with a prominently corticated outline of the interface with normal bone that is in continuity with the lamina dura of the associated tooth.

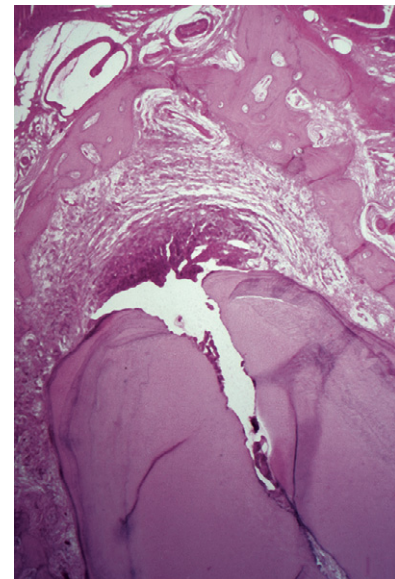
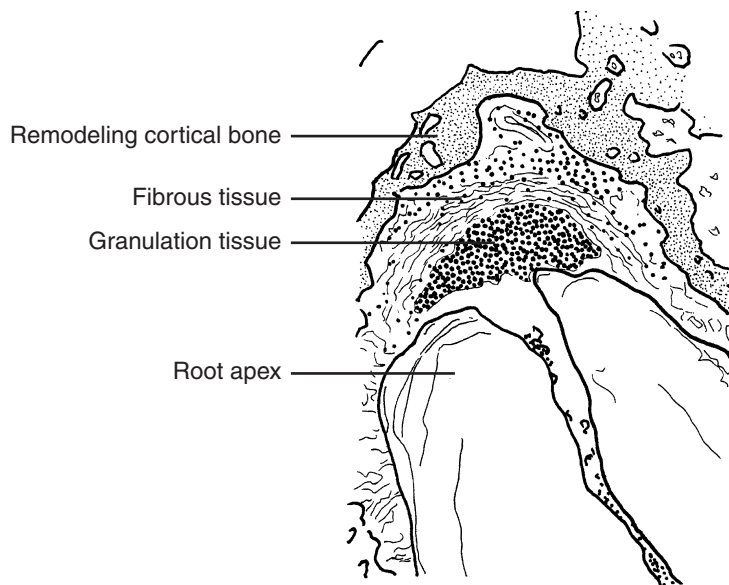


FIGURE 3-25
Periapical granuloma. Microscopic appearance of the early stage of granuloma development, exhibiting granulation tissue at the apical foramen surrounded by fibrous tissue and an outer zone of cortical bone.

and symptomatic, sometimes exhibiting acute exacerbations. Once the cyst has formed, it usually follows a slow but continuous course that can result in the destruction of a large portion of the maxilla or mandible.

RADIOGRAPHIC FEATURES

The periapical cyst is well circumscribed, often with a distinct thin line of cortication separating it from the surrounding bone (Figure 3-27, A). It may be associated with resorption of the apices of the teeth, displacement of the roots, or both. It is distinctly rounded and unilocular and may become very large, resulting in erosion of

the inferior border (Figure 3-27, B) and bulging of the buccal and lingual cortical plates.

HISTOPATHOLOGY

The tissue consists of an outer dense fibrous connective tissue capsule that surrounds a central lumen containing a thick, proteinaceous fluid and cellular debris. The lumen is lined by a nonkeratinized, stratified squamous epithelium containing rete pegs that are generally elongated and branched. Collections of cholesterol-laden macrophages are commonly present, particularly in the early stages of cyst development (Figure 3-28, A). The capsule and the

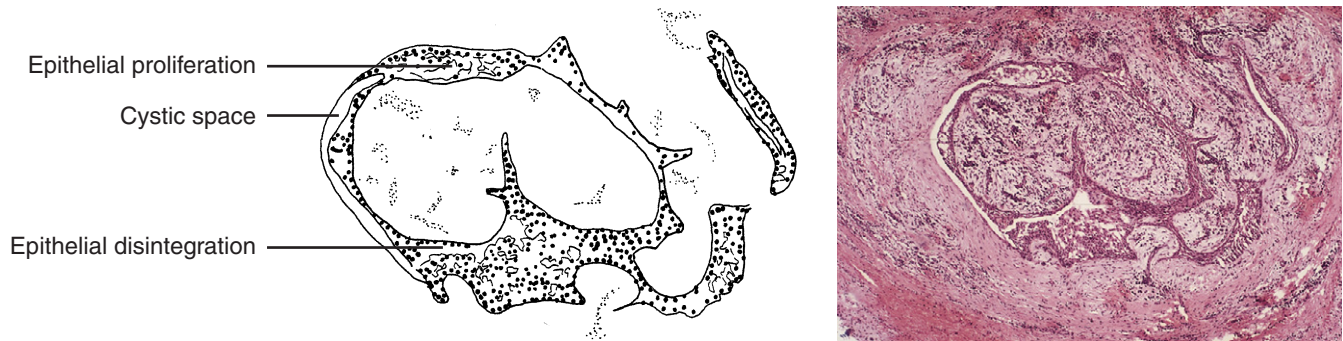


FIGURE 3-26

Periapical cyst. Microscopic appearance of developing cystic lining from proliferating rests of Malassez stimulated by the chronic inflammation of the preceding periapical granuloma.

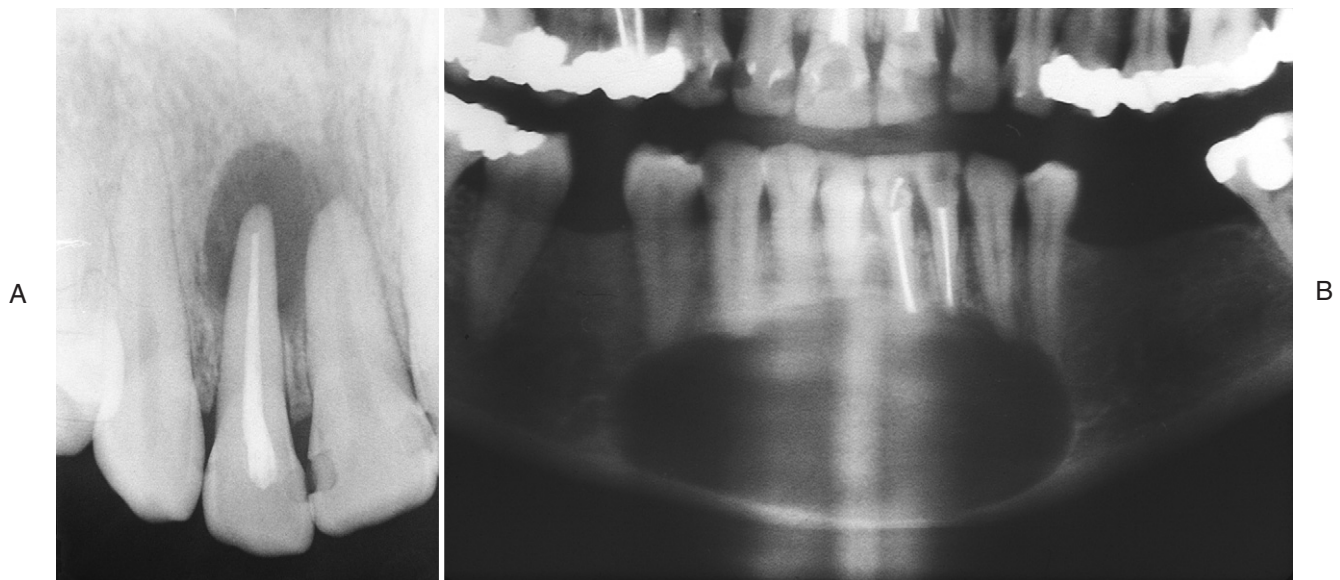
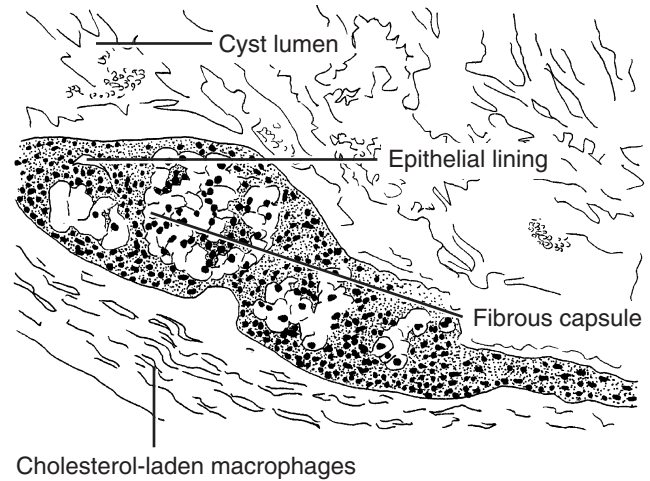
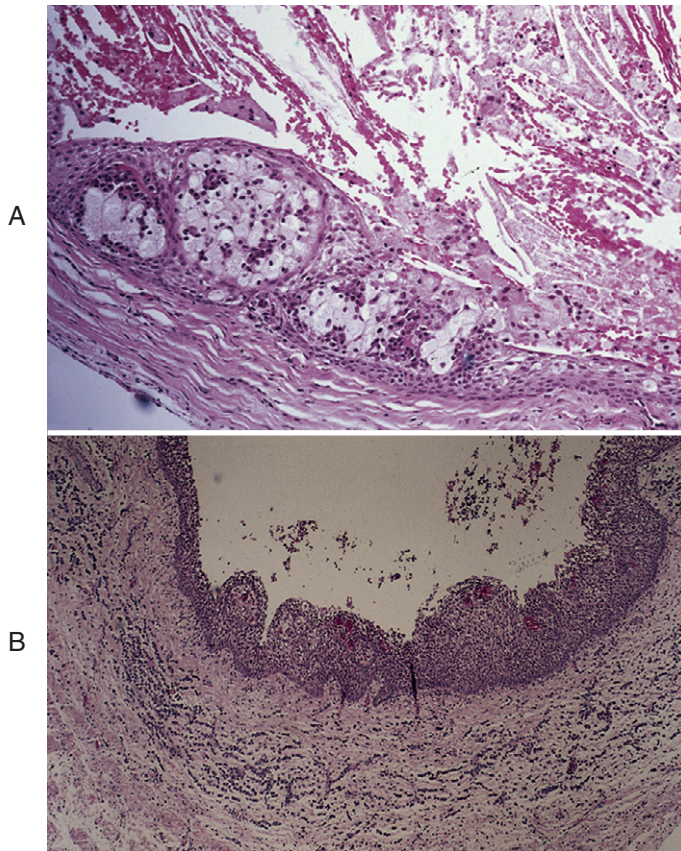


FIGURE 3-27

Periapical cyst. **A**, Radiograph of a small lesion surrounds the apex of a lateral incisor with the distinct line of demarcation separating the lesion from the surrounding bone. **B**, Panoramic radiograph of the anterior mandible containing a large unilocular corticated lesion involving the inferior border.

**FIGURE 3-28**

Periapical cyst. **A**, Microscopic appearance of developing cyst lining with associated cholesterol-laden macrophages within the connective tissue and the lumen. **B**, Matured stratified squamous epithelial lining and fibrous connective tissue capsule with a diffuse infiltrate of lymphocytes and plasma cells surrounding the central lumen.

epithelial lining contain a diffuse infiltration of plasma cells and lymphocytes (Figure 3-28, *B*). Cholesterol crystals surrounded by foreign-body giant cells are a common finding. The presence of eosinophilic refractile hyaline bodies, referred to as *Rushton bodies*, is sometimes found in the intermediate cell layer of the epithelium.

A periapical cyst that remains or forms after the offending tooth has been extracted is referred to as a **residual cyst**. It will have the same radiographic, clinical, and histopathologic features as the periapical cyst.

TREATMENT

Periapical cysts are treated conservatively by enucleation. Recurrence is seldom a problem if the capsule is completely removed. The tissue should be microscopically examined to ensure that it is not one of the other more aggressive odontogenic cysts or a neoplastic lesion. On rare occasions, dysplastic changes and even squamous cell carcinoma have been found in the walls of long-standing cysts.

ACUTE PERIAPICAL CONDITION

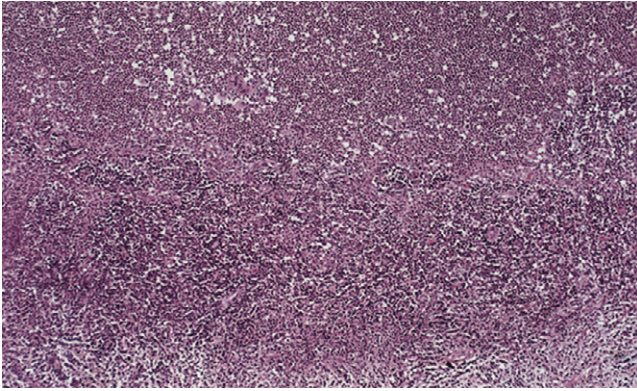
The factors leading to the development of acute lesions at the apex of a tooth are usually one or more of the following:

1. Young tooth with open tubules
2. Rampant caries
3. Closed acute pulpitis
4. Presence of highly virulent microorganisms
5. Weakened host defense system

Under most or all of these circumstances the ensuing inflammatory events happen quickly and cause a great deal of pain. If unchecked, infection and purulent exudate rapidly spread throughout the affected jaw into the adjacent structures and the systemic circulation, where emboli of the infection could lodge in the small capillaries of a number of distant organs or anatomic locations.

PERIAPICAL ABSCESS

The periapical abscess is the initial lesion that develops when the circumstances are adverse. It is probably the most painful patient condition that confronts clinicians and is potentially one of the most dangerous. It is a progression of an acute pulpitis in which exudate extends into the adjacent soft and hard tissues. Because it often contains one or more strains of virulent bacterial organisms, the exudate usually contains potent exotoxins and lytic enzymes capable of rapidly breaking down tissue barriers. Often absent is an opening to allow drainage from the pulp through the crown to the oral cavity, relieving internal pressure within the periodontal

**FIGURE 3-29**

Periapical abscess. Microscopic appearance of an abscess consisting of an outer fibrous wall (*bottom*); an overlying zone of granulation tissue (*center*); and a central core of purulent exudate composed of neutrophils, macrophages, fibrin, and tissue debris (*top*).

membrane. Such internal pressure causes extrusion of the tooth from the socket and rapid extension of the exudate throughout the underlying medullary bone.

CLINICAL FEATURES

Patients with a periapical abscess are in a great deal of pain. Temperature elevation and malaise are common. In most patients the tooth associated with the abscess will extrude from the socket sufficiently to cause occlusal interference and greatly increased pain when it contacts an opposing tooth. In locations where the root apex is in close proximity to the cortex of the overlying alveolar bone, swelling and redness of the area will be present. At this stage the percussion test is most useful in establishing a diagnosis. Although the tooth is relatively insensitive or unresponsive to hot, cold, and electrical stimulation, gently tapping on it produces intense pain.

RADIOGRAPHIC FEATURES

The area around the apex of the tooth initially exhibits a slight widening of the apical periodontal space, with a gradual loss of the distinctness of the adjacent alveolar bone (lamina dura). As the exudate extends into the surrounding medullary bone, the radiographic appearance will reflect the bone loss by exhibiting a faintness of the trabecular pattern and an increased radiolucency. Because a periapical abscess is a rapid lytic process, the radiographic appearance will not exhibit a distinct line of demarcation between the inflammatory process and the normal bone.

HISTOPATHOLOGY

The microscopic features of a periapical abscess are similar to those of an abscess in other parts of the body. An outer thin capsule of fibrous tissue is infiltrated with

lymphocytes and plasma cells. A wide zone of granulation tissue containing a mixture of neutrophils, lymphocytes, plasma cells, and macrophages surrounds a central core of tissue that has undergone disintegration and liquefaction and is composed of purulent exudate (Figure 3-29). In many lesions, bacterial colonies are readily apparent.

OSTEOMYELITIS

OSTEOMYELITIS: An inflammatory process within medullary (trabecular) bone that involves the marrow spaces.

ACUTE OSTEOMYELITIS: A rapidly destructive inflammatory process within bone that consists of granulation tissue, purulent exudate, and islands of nonvital bone (sequestra).

ACUTE OSTEOMYELITIS

Acute osteomyelitis is a destructive lesion of the trabecular bone and bone marrow of an acute inflammatory origin and usually contains virulent strains of bacteria. It is most commonly caused by direct extension of an untreated periapical abscess. Another common cause is a minor traumatic incident involving a mandible that has had its blood supply compromised by previous high doses of radiation for the treatment of a malignancy (osteoradionecrosis). The process of acute osteomyelitis in both cases is rapid if the involved bacterial organisms are particularly virulent or the host's systemic resistance is reduced.

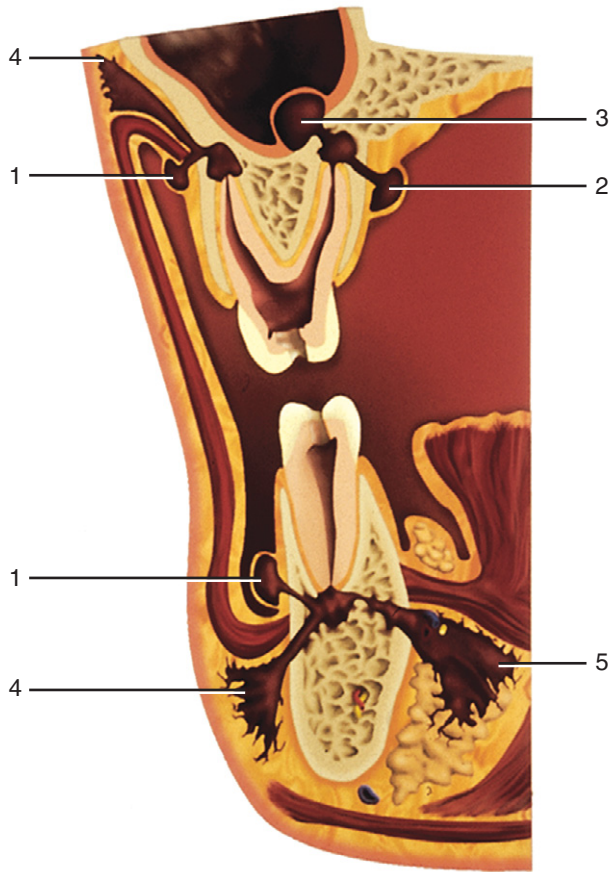
CLINICAL FEATURES

Patients with acute osteomyelitis characteristically have intense pain and become physically ill, especially before the build up of purulent exudate has eroded through the cortical bone, permitting drainage to occur. The pain will return if the exudate continues to accumulate in the soft tissue spaces outside the bone, subsiding only when it finally erodes through the skin or mucosa. As with acute pulpitis, drainage aids resolution and results in a rapid reduction in symptoms, whereas a lack of drainage produces a rapid increase in pain with accompanying pyrexia and malaise. In the mandible the exudate with its accompanying bacterial toxins and lytic enzymes may involve the inferior alveolar canal, producing an alteration in the conductivity of the nerve (Figure 3-30).

This often produces an alteration in the sensation (paresthesia) of the lower lip of the affected side. Paresthesia can cause a great deal of concern, because it is also a common presenting feature when a malignant neoplasm involves the mandible.

RADIOGRAPHIC FEATURES

The radiographic features of acute osteomyelitis are usually not immediately present as the exudate first progresses through the soft tissue component of the

**FIGURE 3-30**

Drainage pathways of acute periapical infections. The location of the various points of drainage is determined by the anatomic location of the root apex. Common locations are (1) surface of gingiva (parulis), (2) palate (palatal abscess), (3) maxillary sinus, (4) soft tissue spaces superior (maxilla) and inferior (mandible) to buccinator muscle (cellulitis), and (5) floor of the mouth (Ludwig angina).

preexisting marrow spaces. It is not until the trabecular bone has undergone a significant amount of resorption that the extent of destruction will be apparent radiographically. Initially the area is faintly visible and eventually appears diffusely blotchy or mottled with indistinct margins (Figure 3-31). Islands of apparently intact bone are often visible in central locations. In reality, these fragments are dead, nonresorbed bone surrounded by wide zones of purulent exudate. An island of dead bone is referred to as a *sequestrum*. It is common for a sequestrum to be externalized by the body and thus appear on the mucosal surface as a loose piece of bone.

HISTOPATHOLOGY

The microscopic features of the involved bone are distinctive. They consist of granulation tissue intermixed with neutrophils, fibrin, and tissue debris surrounding

**FIGURE 3-31**

Acute osteomyelitis. Radiograph of posterior mandible exhibiting the mottled and blotchy pattern of radiolucent and radiopaque areas, indistinct borders, and islands of residual bone (sequestra).

spicules of bone in which the osteocytes have undergone necrosis. In the periphery near the junction with the unaffected bone, the soft tissue consists of a loose, delicate connective tissue with an infiltrate of lymphocytes and plasma cells. This latter finding is also seen in areas of affected bone that are in the early stages of transition to a chronic osteomyelitis that is in the process of resolution.

TREATMENT

The management of acute osteomyelitis is a combination of surgical intervention to establish drainage and the use of high doses of antibiotics that are targeted to the microorganisms involved, which is determined by culture and sensitivity testing.

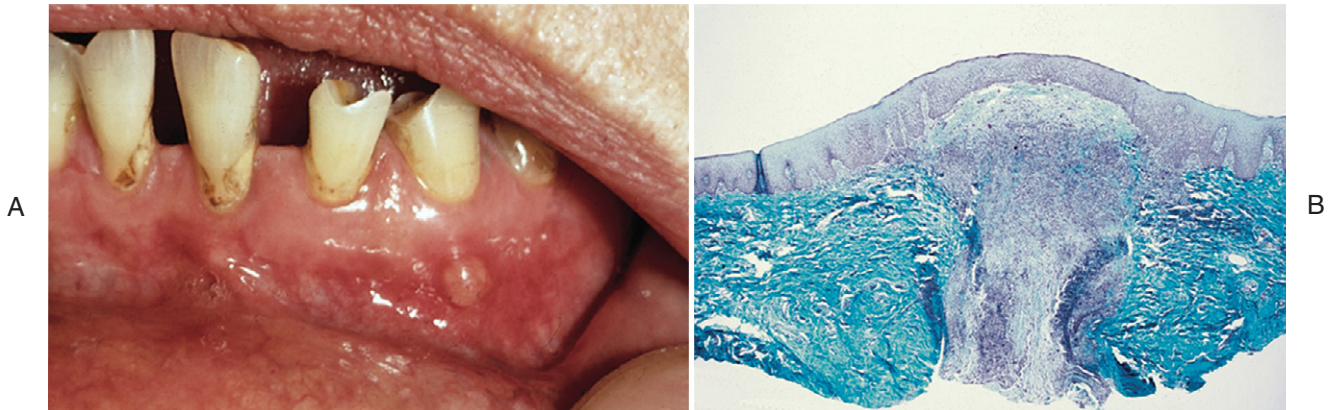
CELLULITIS

CELLULITIS: A painful swelling of the soft tissue of the mouth and face resulting from a diffuse spreading of purulent exudate along the fascial planes that separate the muscle bundles.

SINUS TRACT: A drainage pathway from a deep focus of acute infection through tissue, bone, or both to an opening on the surface.

PARULIS: A sessile nodule on the gingiva at the site where a draining sinus tract reaches the surface.

FISTULA: A drainage pathway or abnormal communication between two epithelium-lined surfaces because of destruction of the intervening tissue.

**FIGURE 3-32**

Parulis. **A**, Patient with a small nodule represents the opening of a draining sinus tract on the gingiva adjacent to a nonvital left mandibular cuspid. **B**, Microscopic appearance of a gingival nodular swelling, demonstrating the central core of purulent exudate (sinus tract) exerting pressure beneath the epithelium that is near the point of rupture (Trichrome stain).

LUDWIG ANGINA: *Cellulitis involving fascial spaces between muscles and other structures of the posterior floor of the mouth that can compromise the airway.*

The term *cellulitis* is actually a misnomer, because the process is not an inflammation of the cells but an acute condition in which purulent exudate, usually accompanied by virulent forms of bacteria, involves the fascial planes between the bundles of facial and perioral muscles. Cellulitis may occur from other causes in the head and neck area, but it is most commonly the result of extension of a periapical abscess into the soft tissue. This occurs when the exudate erodes through the cortical plate of the mandible or the maxilla. When the erosion pathway reaches the gingival surface, it results in a small nodule that enlarges until it ruptures. The site of the opening (stoma) of a sinus tract on the gingiva is commonly termed a *parulis* (Figure 3-32).

Occasionally the exudate tracks onto the palate, producing a large tumorlike mass (Figure 3-33). When a periapical abscess erodes into the maxillary sinus, destroying the intervening bone and lining, and the offending tooth is extracted, a communication between the floor of the sinus and the oral cavity may result. The tract may remain permanently patent, particularly if it becomes lined by epithelium emanating from both sinus (antrum) and oral mucosal linings. This abnormal open communication is termed an *oroantral fistula* (Figure 3-34).

When purulent exudate emanating from a periapical abscess penetrates the alveolar bone and enters the muscle layers, the lytic enzymes from the microorganisms and the acute inflammatory process break down the fascia that normally surrounds and binds the mus-

**FIGURE 3-33**

Palatal abscess. A large fluctuant swelling of the palate caused by the drainage of purulent exudate into the submucosal tissue from an apical area of nonvital premolars.

cle bundles. This breakdown of the fascia allows the exudate to spread throughout the immediate region, greatly increasing the magnitude of the infection.

These patients exhibit extensive swelling of the affected facial region, have considerable discomfort or pain, and develop signs and symptoms of systemic involvement such as elevated temperature, malaise, lethargy, and lymphadenopathy.

Involvement of the soft tissue and muscle overlying the maxilla usually results in periocular swelling and temporary loss of sight on the affected side. When the muscle layers overlying the body of the mandible are involved, patients experience a puffy, pendulous swelling on the left side of the face, closely resembling

mumps. Exudate may extend lingually into the muscle spaces of the posterior floor of the mouth. Such a posterior progression can result in the swelling of the structures in and around the epiglottis. Tissue swelling in this area is life threatening, because it can restrict the airway and result in suffocation if emergency measures are not undertaken immediately. The presence of cel-

lulitis in these locations has historically been referred to as *Ludwig angina*.

Another serious complication of cellulitis is the extension of the exudate into the maxillary cavernous sinus area, resulting in thrombophlebitis. From this location fatal forms of brain abscess or acute meningitis are possible unless rapid intervention is undertaken.

CHRONIC OSTEOMYELITIS

Chronic osteomyelitis differs greatly from the acute types by inducing bone to form and become denser. It occurs in response to a low-grade inflammatory process rather than the intense and destructive inflammation caused by virulent bacteria. A great deal of variation is seen in the chronic forms of bone inflammation. Typically, little or no pain is felt. In many cases the irritant may be so mild it stimulates the osteocytes, inducing the trabecular bone to become denser and even lay down additional bone, which results in a reduction of the marrow spaces. The area will radiographically appear mottled and more radiopaque than normal. This process is histologically referred to as **osteosclerosis**. It may be confined to an area around the root of a tooth (Figure 3-35, A and B) or be present where a tooth previously existed (Figure 3-35, C). These localized changes in the bone are referred to



FIGURE 3-34
Oroantral fistula. An open communication between the maxillary sinus (antrum) and the oral cavity is present on the edentulous alveolar ridge after the extraction of a molar with a long-standing periapical lesion that involved the sinus floor.



FIGURE 3-35
Chronic osteosclerosis. **A**, Radiograph of an area of uniform increase in bone density located apically to the maxillary lateral incisor. **B**, Radiograph of a localized area of radiolucency with central nodular radiopacities. **C**, Radiograph of an area of nodular radiopacities in the location of a previously existing tooth. These lesions have also been termed *focal chronic sclerosing osteomyelitis*.

as **focal chronic sclerosing osteomyelitis**. In other instances the osteosclerosis may involve larger areas of bone (Figure 3-36) or edentulous areas in one or more quadrants. These conditions are referred to as **diffuse chronic sclerosing osteomyelitis**.

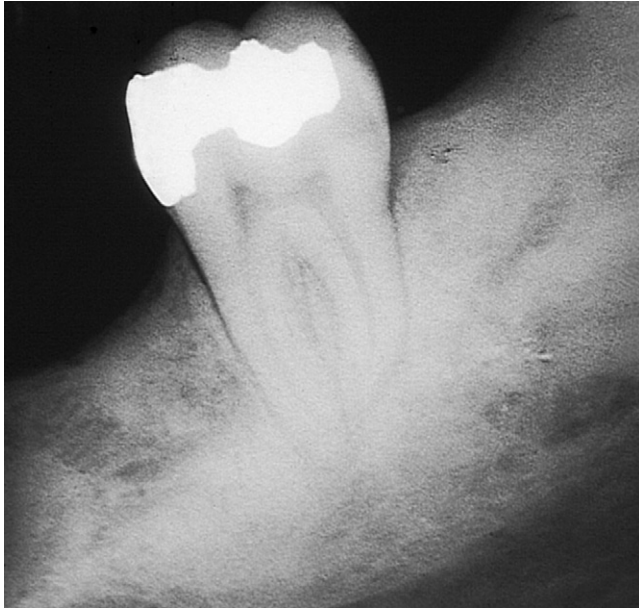


FIGURE 3-36
Diffuse chronic sclerosing osteomyelitis. A portion of a large diffuse area of radiopacity of the mandible that has indistinct boundaries indicative of increased bone density.

GARRÉ OSTEOMYELITIS

Garré osteomyelitis is an unusual hyperplastic reaction of the periosteum to a chronic osteomyelitis of the posterior mandible that is unique to young patients. The correct terminology is **chronic osteomyelitis with proliferative periostitis**; however, because this descriptive term is long and cumbersome, it is seldom used clinically.

CLINICAL FEATURES

In the jaws, Garré osteomyelitis is most frequently associated with advanced acute caries in young patients that has progressed to pulpitis and a periapical lesion. To become a Garré osteomyelitis the inflammatory response must extend through the bone to the outer surface, stimulating the periosteum to thicken and lay down excess layers of new bone. In other situations this form of osteomyelitis occurs when the free gingival margin remains above the height of contour of the tooth, resulting in food impaction of the deepened gingival sulcus; a constant low-grade infection persists that stimulates the periosteum.

Patients who develop this form of osteomyelitis are characteristically in the age group that occurs shortly before the mixed dentition stage or immediately afterward. They slowly exhibit a diffuse or focal enlargement of an area of the mandible, usually posteriorly (Figure 3-37). The other common cause of this unique process is a molar that is unable to fully erupt (Figure 3-38). Upon palpation the area will be as hard

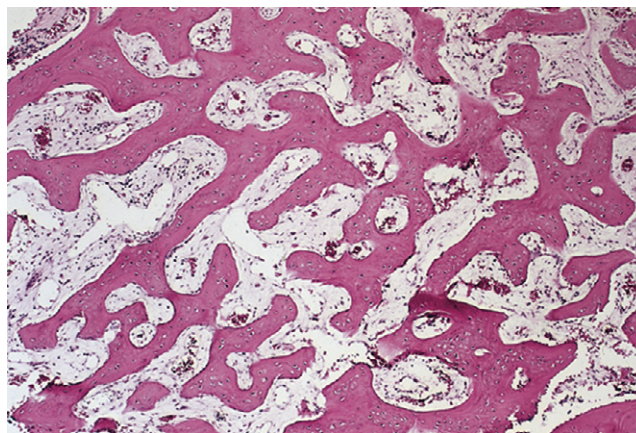


FIGURE 3-37

Garré osteomyelitis. **A**, Young patient with an enlargement of the left side of the face over the mandible. **B**, Lateral radiograph of the patient in **A** reveals a large mixed radiolucent and radiopaque area indicative of excess bone formation of the mandible. (Courtesy Dr. David G. Gardner.)

**FIGURE 3-38**

Garré osteomyelitis. An occlusal radiograph of excess layers of bone on the buccal plate (“onion skin”) opposite a partly erupted second molar.

**FIGURE 3-39**

Garré osteomyelitis. Microscopic appearance of the periphery of excess porous bone layers with intervening cellular connective tissue and without cortex formation.

as the normal surrounding bone, and the patient will not exhibit pain when the area is slightly palpated. The area is usually asymptomatic.

RADIOGRAPHIC FEATURES

A radiograph taken using an occlusal projection will demonstrate the characteristic multiple thin layers of new bone, referred to as an “onion skin” appearance. The trabecular bone will also exhibit the characteristic diffuse mottling of a chronic osteomyelitis.

HISTOPATHOLOGY

The microscopic features of the reactive bone that forms in response to the stimulated periosteum is less dense than normal cortical bone and deposited in a layered pattern. The trabecular spaces are wide and occupied with a cellular connective tissue (Figure 3-39).

TREATMENT

The condition slowly reverts to normal after the source of infection is identified and resolved. Sometimes extraction of the offending tooth or surgical recontouring of the tissue in the molar area is necessary.

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4 Bone Lesions

CHAPTER OUTLINE

BENIGN FIBRO-OSSEOUS LESIONS

Cemento-Osseous Lesions
 Periapical Cemental Dysplasia
 Florid Cemento-Osseous Dysplasia
 Fibrous Dysplasia
 Juvenile Fibrous Dysplasia
 Adult Monostotic Fibrous Dysplasia
 Polyostotic Fibrous Dysplasia
 Cherubism

METABOLIC CONDITIONS

Paget Disease
 Hyperparathyroidism
 Osteopetrosis
 Osteogenesis Imperfecta

BENIGN TUMORS

Torus, Exostosis, and Osteoma
 Torus Palatinus
 Torus Mandibularis
 Exostosis
 Osteoma
 Osteoid Osteoma and Osteoblastoma
 Cemento-Ossifying Fibroma
 Giant Cell Lesions
 Peripheral Giant Cell Granuloma
 Central Giant Cell Lesion
 Aneurysmal Bone Cyst
 Traumatic Bone Cyst
 Langerhans Cell Histiocytosis

MALIGNANT TUMORS

Osteogenic Sarcoma
 Chondrosarcoma
 Ewing Sarcoma

ADDITIONAL KEY TERMS

Alkaline phosphatase
 Focal cemento-osseous dysplasia
 Gardner syndrome
 Jaffe syndrome
 McCune-Albright syndrome
 Osteitis deformans
 Osteolytic
 Osteosclerotic
 Urinary hydroxyproline



Obtaining universal agreement on the classification and terminology of bone lesions of the mandible and maxilla has been difficult. In this chapter the conditions are categorized under four general headings: (1) benign fibro-osseous lesions, (2) metabolic conditions, (3) benign tumors, and (4) malignant tumors. Except for the malignant tumors, this categorization may not be accurate in light of future knowledge because the nature of some of the benign fibro-osseous lesions is not yet known. Moreover, the altered biochemical pathways of many of the metabolic conditions are not completely understood, and not all the lesions designated as benign bone tumors are true neoplasms.

BENIGN FIBRO-OSSEOUS LESIONS

BENIGN FIBRO-OSSEOUS LESIONS: A collection of nonneoplastic intraosseous lesions that replace normal bone and consist of a cellular fibrous connective tissue within which nonfunctional osseous structures form.

Lesions that develop within the jaws by replacing normal trabecular bone and marrow with cellular fibrous tissue and randomly oriented mineralized structures have conveniently been included under the general heading of *benign fibro-osseous lesions*.

Different names have been applied to the lesions in this group, attesting to the lack of knowledge of their true identity. In the mandible and maxilla, a subgroup of the most common of these lesions is collectively referred to as the *cemento-osseous dysplasias*. They are so named because they all contain a combination of spherical calcifications believed to be of cemental origin (cementicles) and randomly oriented osseous structures resembling detached fragments of trabecular bone. The two other conditions in this category are (1) fibrous dysplasia and (2) cherubism. Although the latter two conditions are far less common, they are of greater clinical significance because of their potential to achieve a large size, distort the face, and produce extensive malocclusion (Table 4-1).

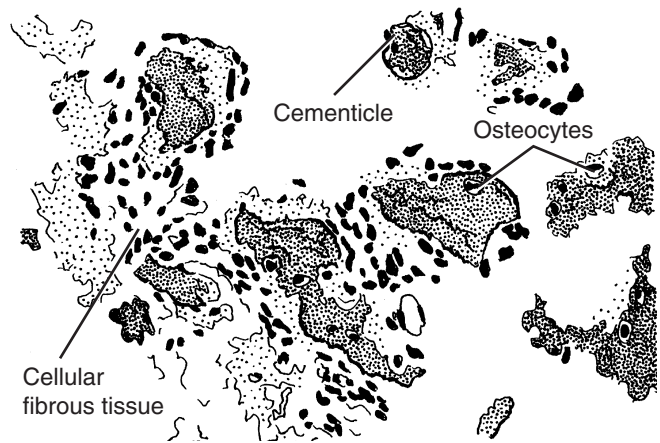
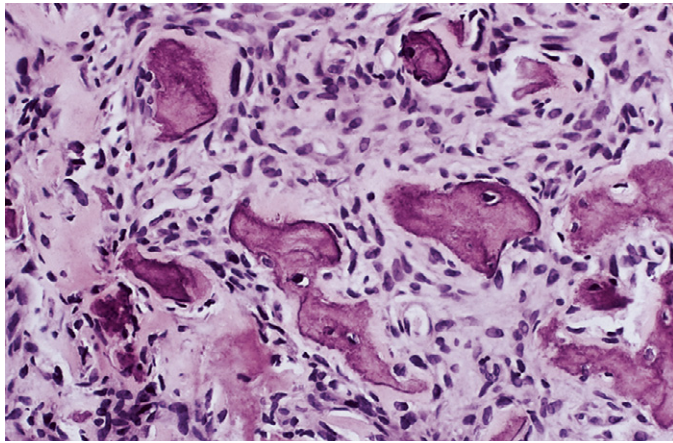
CEMENTO-OSSEOUS LESIONS

CEMENTO-OSSEOUS LESIONS: Benign fibro-osseous lesions of the jaws closely associated with the apices of teeth and containing amorphous spherical calcifications thought to resemble an aberrant form of cementum; lesions are usually without signs or symptoms.

Until recently, these lesions were included in the classification of odontogenic tumors of connective tissue origin. They were considered odontogenic because the spherical calcifications that are often prominent in the connective tissue were thought to be an aberrant form

Table 4-1 Fibro-Osseous Lesions of Jaws

Lesion	Clinical Features	Radiographic Features
PERIAPICAL CEMENTAL DYSPLASIA	Nonexpansile	Lucent; lucent/opaque; opaque
	Nonsymptomatic	Distinct periodontal membrane
	Anterior mandible	Lucent peripheral zone
	Middle-aged women	Periapical location only
	Vital teeth	
FLORID CEMENTO-OSSEOUS DYSPLASIA	Nonexpansile	Mixed lucent and opaque lesions
	Nonsymptomatic	"Cotton ball" appearance
	One to four jaw quadrants	Occupies entire jaw
	Middle-aged African-American women	
FIBROUS DYSPLASIA	Expansion of cortices	Early—lucent area
	One or many bones	Late—"ground glass"
	Usually self-limiting	Lamina dura usually lost
	Mild malocclusion	
CHERUBISM	Hereditary	Early—cystic lucencies
	Distinct facies	Late—"ground glass"
	Bilateral/symmetric	Displaced teeth and buds
	Childhood to late teens	Expanded arches
	Self-limiting	
	Severe malocclusion	

**FIGURE 4-1**

Cemento-osseous lesion. Microscopic features are common to all cemento-osseous lesions and demonstrate spherical (cementicle) and irregularly shaped calcifications containing occasional osteocytes (osseous) in a background of typical cellular loose fibrous connective tissue.

of cementum originating from the periodontal membrane (Figure 4-1). Although these lesions occur most commonly in the jaws, lesions with similar histologic features are found in other bones.

Periapical Cemental Dysplasia

PERIAPICAL CEMENTAL DYSPLASIA: *Asymptomatic diffuse periapical radiolucent and radiopaque areas, primarily of the anterior mandible, in which cemento-osseous tissue replaces the normal architecture of bone.*

The term *periapical cemental dysplasia* (PCD) was first used in the 1971 World Health Organization (WHO) classification of odontogenic tumors, where it was included as one of the four types of cementoma. Before that time, names such as “multiple cementoma,” “periapical fibrous dysplasia,” “periapical osteofibrosis,” and “localized fibro-osteoma” were applied to the lesion. In the 1992 WHO classification, PCD was removed from the classification of odontogenic tumors and placed among the fibro-osseous bone lesions. PCD is not a true neoplasm but a dysplastic condition in which multiple focal areas of normal bone and marrow are replaced by cellular connective tissue lesions with limited growth potential. The lesions attain a fixed size and later undergo a maturation process that culminates in the formation of multiple dense calcified (sclerotic) intraosseous nodules.

CLINICAL FEATURES

PCD is usually discovered accidentally during evaluation of routine radiographs or during an investigation of another problem. No symptoms or visible external alterations of the involved bone occur. Lesions are primarily found in middle-aged women, with a higher incidence among African Americans; it is rarely found in

patients less than 20 years of age. It is most frequently located below the apices of the mandibular incisors, but can be more widely distributed, occurring within other areas of the arch or the opposing arch. The teeth overlying the lesions remain vital. Buccal or lingual expansion of the cortices is usually absent.

RADIOGRAPHIC FEATURES

PCD has three radiographic features that indicate stages from early formation to maturation: (1) osteolytic, (2) cementoblastic, and (3) mature.

Osteolytic Stage

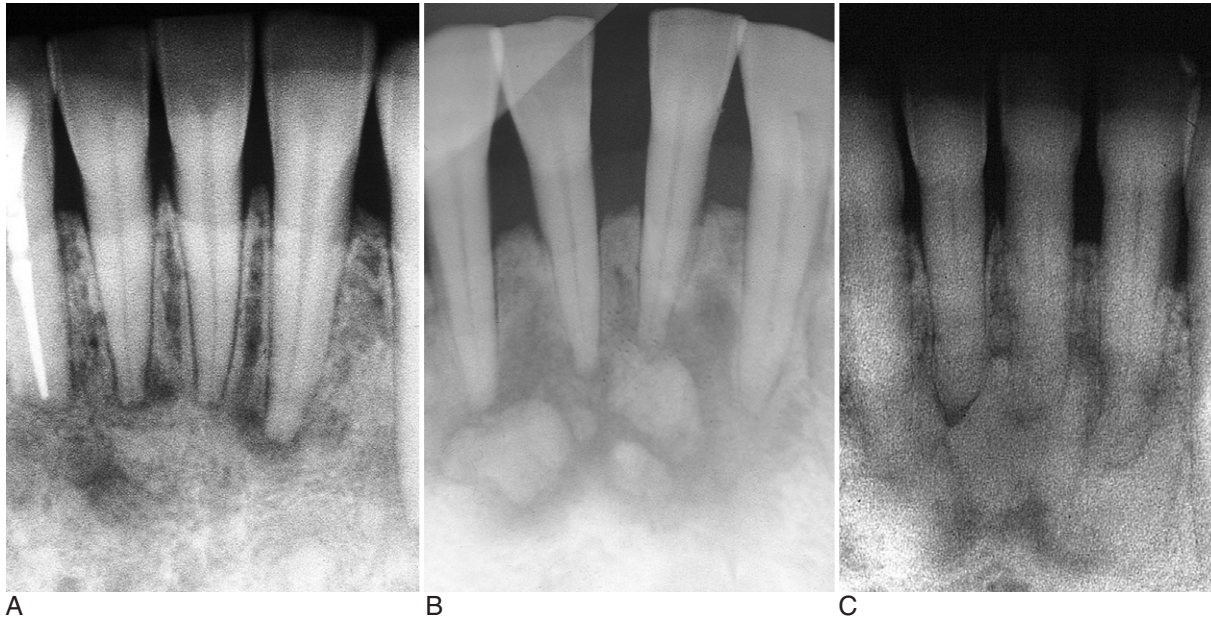
In this early stage, lesions are well-defined radiolucencies at the apex of one or more teeth. The radiolucencies surround the tip of the root and are usually indistinguishable from an inflammatory periapical lesion of pulpal origin (Figure 4-2, A). In most cases the teeth are free from caries or restorations but may be coincidentally involved. Thus before endodontic treatment or extraction is performed, it is necessary to undertake pulpal evaluation of the associated teeth.

Cementoblastic Stage

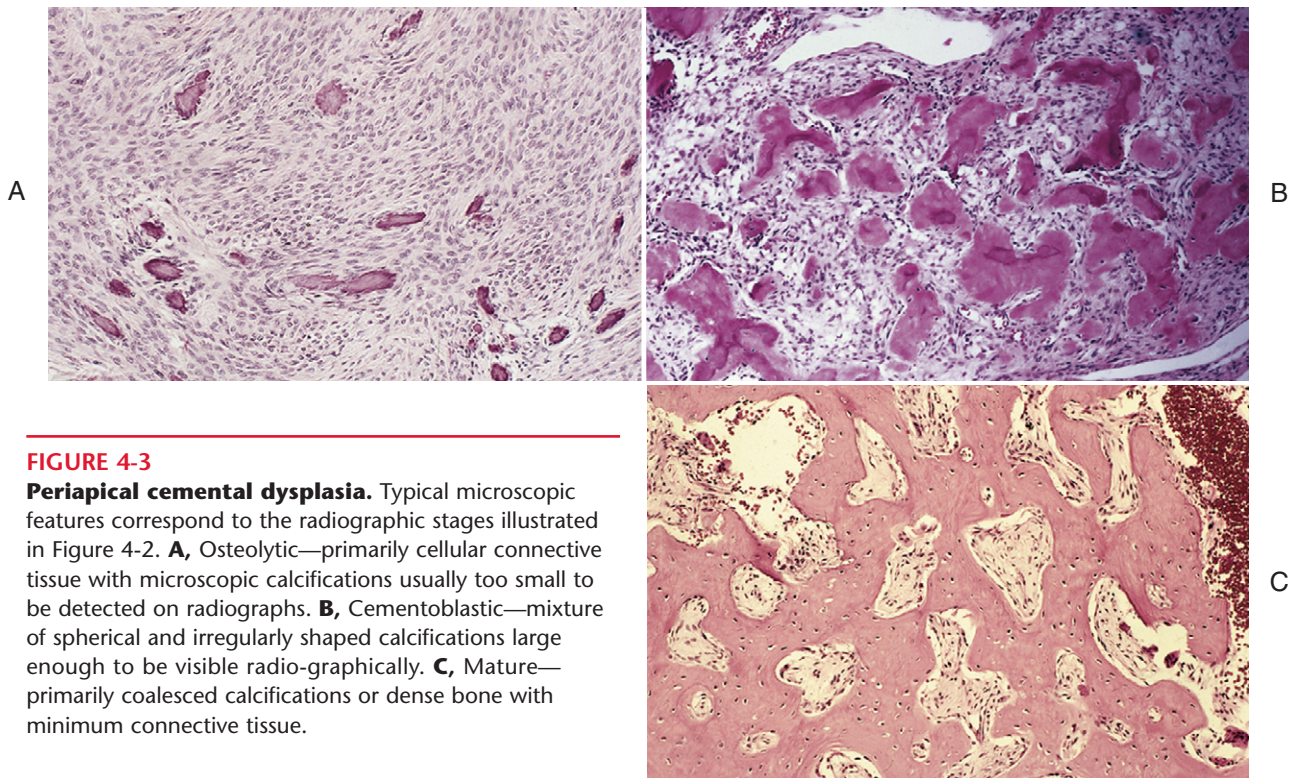
The cementoblastic stage displays similarly sized lesions and a demarcated border with radiolucencies containing nodular radiopaque deposits (Figure 4-2, B).

Mature Stage

After lesions have reached this stage, they are well-defined, dense radiopacities that usually exhibit some nodularity. The periodontal membrane can be seen separating the lesion from the tooth. Each radiopaque nodule has a thin radiolucent zone around its periphery that separates it from the surrounding bone and nearby teeth (Figure 4-2, C).

**FIGURE 4-2**

Periapical cemental dysplasia. Radiographic features of osteolytic (**A**), cementoblastic (**B**), and mature stages (**C**).

**FIGURE 4-3**

Periapical cemental dysplasia. Typical microscopic features correspond to the radiographic stages illustrated in Figure 4-2. **A**, Osteolytic—primarily cellular connective tissue with microscopic calcifications usually too small to be detected on radiographs. **B**, Cementoblastic—mixture of spherical and irregularly shaped calcifications large enough to be visible radiographically. **C**, Mature—primarily coalesced calcifications or dense bone with minimum connective tissue.

HISTOPATHOLOGY

The histologic appearance changes with the stage of maturation. The **osteolytic** stage consists primarily of cellular connective tissue replacing the normal trabecular bone with calcified structures of insufficient size to be observed radiographically (Figure 4-3, A). The cementoblastic stage

has the same connective tissue component, but displays a mixture of spherical calcifications and irregularly shaped deposits of osteoid and mineralized bone. These calcified and mineralized structures are surrounded by osteoblasts containing osteocytes (Figure 4-3, B). Tissue from the matured stage is composed almost entirely of

coalesced spherical calcifications and sclerotic mineralized bone with little connective tissue (Figure 4-3, C).

TREATMENT

After a diagnosis of PCD is made, no further treatment is necessary.

Florid Cemento-Osseous Dysplasia

FLORID CEMENTO-OSSEOUS DYSPLASIA: *Diffuse asymptomatic, radiopaque and radiolucent intraosseous areas of cemento-osseous tissue that involve one or both arches.*

Florid cemento-osseous dysplasia (FCOD) is a more extensive form of PCD. It may be confined to one quadrant or involve all four quadrants. It has been added to the classification of oral disease, replacing the previous diagnosis of *diffuse sclerosing osteomyelitis* when no evidence of infection or other bone inflammation is present.

CLINICAL FEATURES

Patients are most commonly middle-aged African-American women, although lesions in women of other ethnic groups have occasionally been reported. It is uncommon in men. External signs or symptoms are generally absent with lesions found on routine radiographic evaluation. Patients will experience pain or discomfort if involved areas become secondarily infected as a result of periapical infection or after an extraction. The areas of dense bone have reduced vascularity and are less able to cope with the usual transient infection. On occasion, after patients become edentulous, some of the dense sclerotic bone nodules break through the surface, because they do not resorb

at the same rate as normally vascularized alveolar bone. These sequestra cause much discomfort and act as a portal of entry for bacteria that can cause an acute osteomyelitis.

RADIOGRAPHIC FEATURES

The radiographic appearance of FCOD is dramatic, consisting of multiple radiolucent and radiopaque intraosseous lesions. The lesions are diffusely distributed and contain faint nodular radiopacities reminiscent of clouds or cotton balls. Some large, purely radiolucent areas may be interspersed among the radiopacities. Lesions occupy the complete thickness of the bone and are found from the alveolar crest to the inferior border (Figure 4-4, A). A solitary lesion is occasionally present, usually in a molar area. Such a lesion has recently been designated as **focal cemento-osseous dysplasia** (Figure 4-4, B).

HISTOPATHOLOGY

Tissue from the involved area is composed of cellular connective tissue containing many small and large spherical calcifications and large nodules of dense bone (Figure 4-5). A zone of connective tissue usually separates the lesions from the surrounding bone. Occasionally, areas of traumatic (hemorrhagic) bone cyst can be observed in the connective tissue of the lesions.

TREATMENT

FCOD lesions are not treated unless the dense bone nodules become secondarily infected and produce osteomyelitis in the area. Treatment of the complicating osteomyelitis consists of débridement, drainage, and antibiotics.

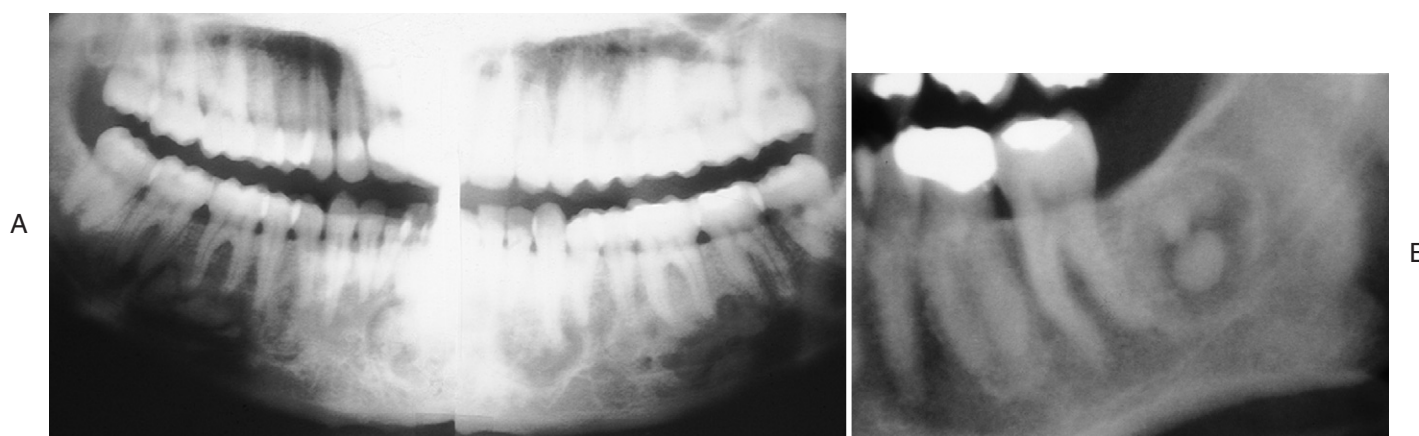
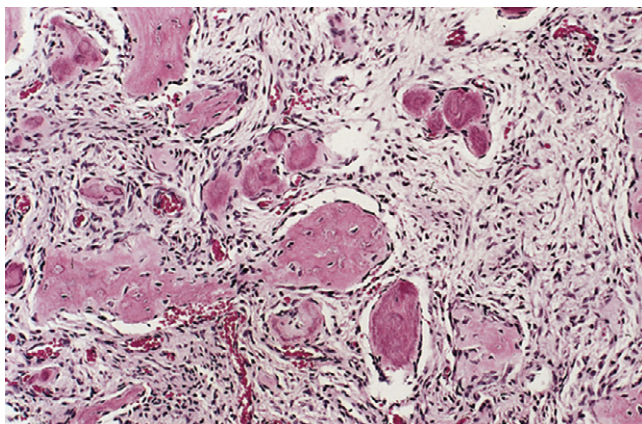


FIGURE 4-4

A, Florid cemento-osseous dysplasia. Panoramic radiograph demonstrating multiple mixed radiopaque and radiolucent intraosseous lesions throughout the mandible. **B, Focal cemento-osseous dysplasia.** Radiograph of solitary, well-demarcated, mixed radiopaque and radiolucent lesion in the posterior mandible.

**FIGURE 4-5**

Florid cemento-osseous dysplasia. Microscopic features consisting of a cellular connective tissue containing spherical and irregular calcified structures similar to other cemento-osseous lesions.

BOX 4-1

Clinical Forms of Fibrous Dysplasia of the Jaws

MONOSTOTIC

Juvenile
Juvenile, aggressive
Adult

POLYOSTOTIC

Craniofacial
McCune-Albright syndrome
Jaffe syndrome

FIBROUS DYSPLASIA

FIBROUS DYSPLASIA: An asymptomatic regional alteration of bone in which the normal architecture is replaced by fibrous tissue and nonfunctional trabeculae-like osseous structures; lesions may be monostotic or polyostotic, with or without associated endocrine disturbances.

Fibrous dysplasia is a poorly understood nonneoplastic disease of bone in which fibro-osseous lesions replace the normal trabecular bone, altering its size and shape. It may involve only a single bone (monostotic) or multiple bones (polyostotic). Fibrous dysplasia is not considered a true neoplasm, because it is self-limiting. It begins as a fibrous replacement of the medullary bone, which in turn is gradually replaced by a metaplastic woven bone that eventually matures into dense lamellar bone. The condition is most commonly found in a single bone (monostotic) in juveniles and young adults, but an adult-onset form is occasionally encountered. When multiple bones are involved (polyostotic), fi-

brous dysplasia commonly occurs as part of the **McCune-Albright syndrome**. The syndrome is associated with a mutation in the *GNAS1* gene at 20q13.2; in addition to polyostotic fibrous dysplasia, it features skin pigmentations and endocrine dysfunctions. When, on rare occasions, the polyostotic form of fibrous dysplasia occurs in the absence of endocrine disturbances, it has been termed *Jaffe syndrome* (Box 4-1).

Juvenile Fibrous Dysplasia

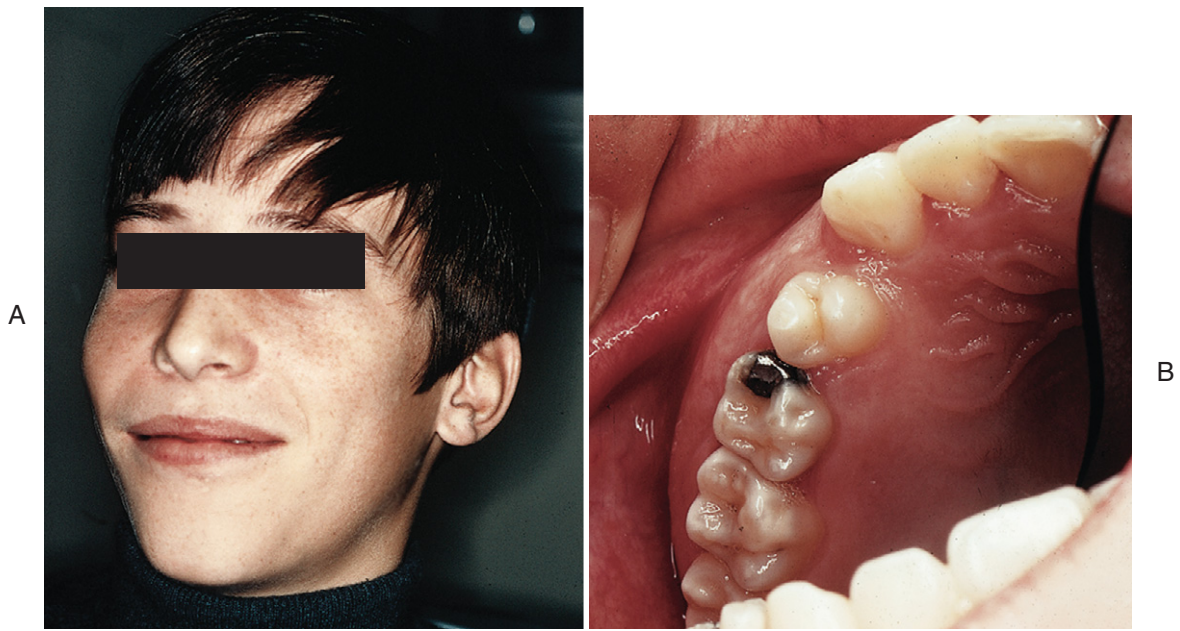
In the head and neck area, juvenile fibrous dysplasia is the most common type of monostotic regional deformity. It is a slow-growing regional distortion that usually enlarges proportionately with the affected bone. The regional overgrowth continues until general body growth ceases in the late teens or early twenties. An uncommon form known as *aggressive juvenile fibrous dysplasia* grows at a faster rate than the affected bone, producing major, often grotesque deformity that results in loss of function. Another uncommon form of fibrous dysplasia is *craniofacial fibrous dysplasia*, a component of polyostotic fibrous dysplasia in which lesions occur in the bones of the jaws and cranium.

CLINICAL FEATURES

Juvenile fibrous dysplasia begins in early to late childhood. Initially it may go unnoticed, because the asymmetry may be so mild as to be considered within normal ranges (Figure 4-6). The maxilla is affected more often than the mandible. Eventually the lesion becomes noticeable, although pain or discomfort is absent. Teeth are often displaced, rotated, or malaligned. This results in severe malocclusion that often requires orthodontic intervention, even though treatment of the bone enlargement is unnecessary. The aggressive form of juvenile fibrous dysplasia becomes symptomatic if the lesion is traumatized and ulcerated because of impingement by the teeth during mastication. In the maxilla the aggressive form often extends to the floor of the orbit and the nasal passages, interfering with both sight and breathing. Treatment to alleviate gross distortion and to restore function is often required in these lesions.

RADIOGRAPHIC FEATURES

The radiographic appearance varies with the stage of maturity of the lesion. In early lesions the area may be radiolucent, becoming more radiopaque as more bone is formed. A mature lesion retains none of the normal architecture of trabecular bone, having replaced it with abnormal bone that produces a “ground glass” or “orange peel” pattern on radiographs (Figure 4-7). No line of demarcation exists, because the lesion blends with

**FIGURE 4-6**

Juvenile fibrous dysplasia. **A**, Facial asymmetry caused by expansile lesion of right maxilla. **B**, Diffuse buccal and lingual expansion of right alveolar process exhibiting displacement of first premolar and retained primary molar. (Courtesy Dr. Alan M. Coote and Dr. Douglas W. Stoneman.)

**FIGURE 4-7**

Juvenile fibrous dysplasia. Radiograph of maxillary alveolar process exhibiting "ground glass" or "orange peel" appearance.

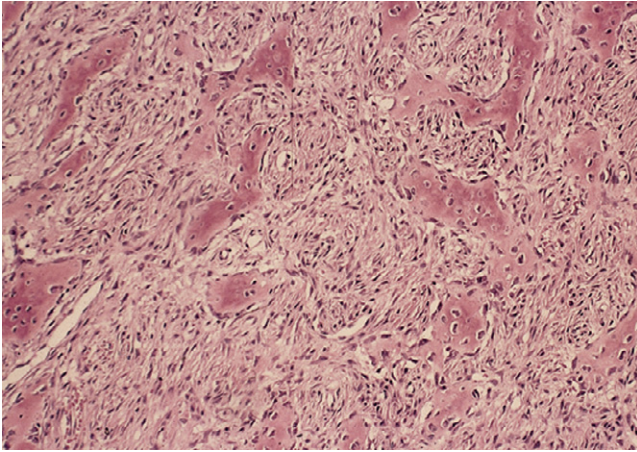
the surrounding bone. Expansion of the cortical plates and displacement of tooth roots is common. The lamina dura is usually obscured and the cortical plates thinned.

HISTOPATHOLOGY

The composition of the tissue differs throughout the various stages until maturity is reached. Initially it is composed of cellular connective tissue that has replaced the normal trabeculae and marrow. Gradually, irregular islands of metaplastic bone emerge from the fibrous tissue background (Figure 4-8). The new bone has a woven pattern when viewed with polarized light. In the jaws, some spherical calcifications may be included with the abnormal bone formation. Eventually the bony component predominates the lesion with much of the bone and collagen matrix developing a lamellar pattern. By adulthood the lesion usually matures, and bone may be somewhat normal.

TREATMENT

Treatment is pursued only when lesions are cosmetically unacceptable or interfere with sight, breathing, mastication, or speech. Some clinicians believe that constant surgical osteoplasty of a lesion will accelerate

**FIGURE 4-8**

Juvenile fibrous dysplasia. Microscopic appearance of cellular fibrous connective tissue with irregularly shaped islands of osteoid and bone.

it from an indolent to an aggressive course, resulting in greater distortion than might otherwise occur. It is important to biopsy lesions, because other, more serious diseases may have a similar clinical and radiographic appearance. Most lesions of the normal form of juvenile fibrous dysplasia do not require treatment until the patient has reached early adulthood. At this time the degree of cosmetic improvement that can be accomplished by surgery is assessed. Lesions should not be treated by radiotherapy in an attempt to halt growth, because the risk of a malignancy in later life is greatly enhanced.

Adult Monostotic Fibrous Dysplasia

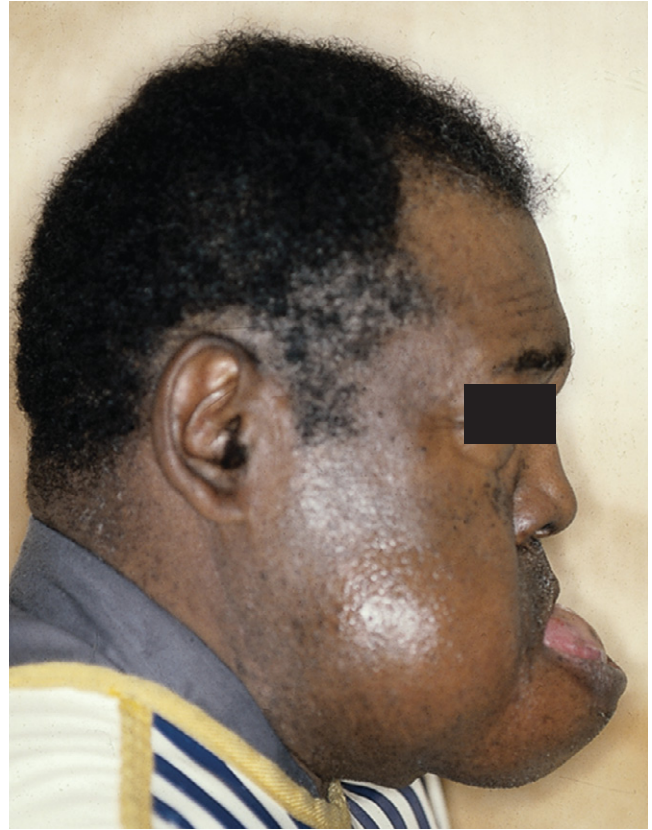
Adult monostotic fibrous dysplasia is a rare form of fibrous dysplasia occurring spontaneously in adulthood. It resembles an ossifying fibroma in many ways but must be separated from it because treatment is very different.

CLINICAL FEATURES

Adult monostotic lesions resemble those of mature juvenile fibrous dysplasia. The affected area presents as an asymptomatic diffuse expansion of the cortices (Figure 4-9). Some movement of teeth within the area may occur.

RADIOGRAPHIC FEATURES

The radiographic appearance of adult lesions is usually less homogeneous than juvenile fibrous dysplasia, exhibiting a mixed radiolucent and radiopaque “cotton

**FIGURE 4-9**

Adult monostotic fibrous dysplasia. Clinical appearance of an unusually large lesion of the mandible.

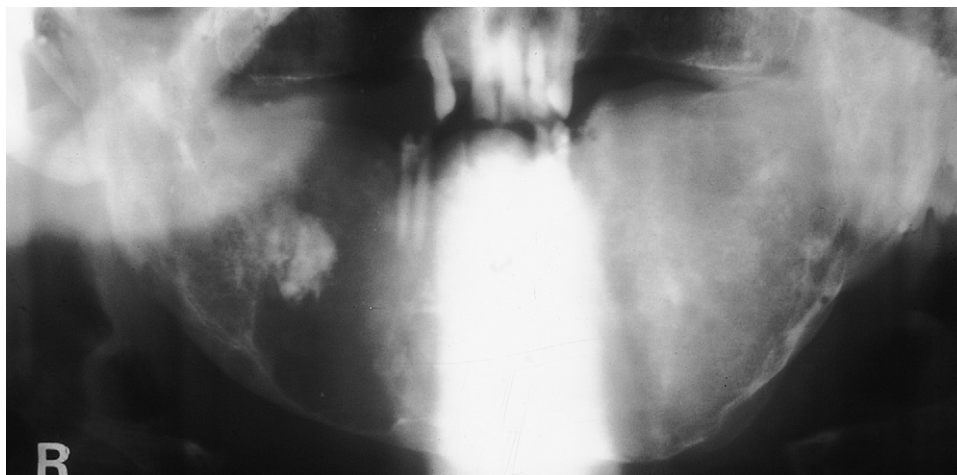
ball” pattern. As with other forms of the disease, individual lesions blend with the surrounding bone. Expansion and thinning of the cortical plates is usually evident (Figure 4-10).

HISTOPATHOLOGY

The tissue contains some areas in which cellular fibrous connective tissue predominates and other areas dominated by immature metaplastic bone with a woven pattern. Of diagnostic importance is the blending of lesional tissue with surrounding normal bone and the cortical plates—a feature that separates it from ossifying fibroma.

TREATMENT

Treatment of adult monostotic fibrous dysplasia differs from the juvenile form, because it is not self-limiting. In adults, attempts are made to completely remove smaller lesions and halt the progression of larger ones with continuous conservative treatment.

**FIGURE 4-10**

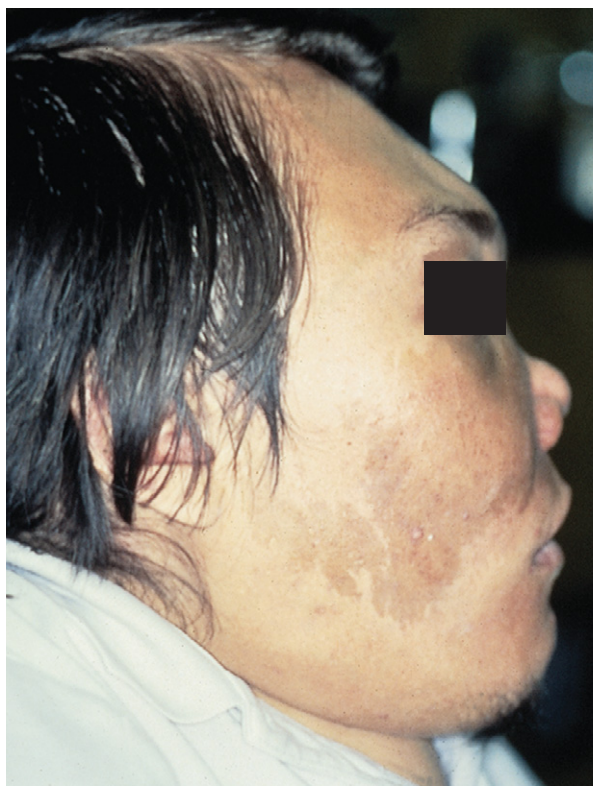
Adult monostotic fibrous dysplasia. Panoramic radiograph of lesion in Figure 4-9 revealing massive expansion of the mandible and the “ground glass” appearance of the involved bone.

Polyostotic Fibrous Dysplasia

Polyostotic fibrous dysplasia is usually accompanied by skin pigmentation and endocrine dysfunction. Bone lesions may be confined to the craniofacial area or distributed diffusely throughout the skeleton.

CLINICAL FEATURES

The presence of expansile lesions in multiple bones (particularly the craniofacial bones) gives the patient an unpleasant appearance. Many patients will also have large light-brown pigmentations termed *café au lait spots* on the



A

FIGURE 4-11

Polyostotic fibrous dysplasia. **A**, Clinical appearance of patient exhibiting disproportionate bone growth caused by multiple fibrous lesions of the craniofacial bones and café au lait pigmentations. **B**, Expansile lesions of the mandible and maxilla are evident in all quadrants.



B

torso, particularly the back, buttocks, and sacral areas. The pigmented areas have a jagged periphery, in contrast to pigmented skin areas found in multiple neurofibromatosis, where the periphery is smooth (Figure 4-11). The bones most commonly involved are the ribs, cranium, maxilla, femur, tibia, and humerus. When endocrine dysfunction is present (McCune-Albright syndrome), manifestations often begin in early childhood. The most notable and concerning is precocious sexual development in young women, consisting of premature vaginal bleeding, breast development, and emergence of axillary and pubic hair. Other endocrine dysfunctions include thyrotoxicosis, pituitary gigantism, and Cushing syndrome. The array of abnormalities is highly variable from case to case. Fortunately, McCune-Albright syndrome is uncommon.

HISTOPATHOLOGY

The microscopic appearance of bone lesions of polyostotic fibrous dysplasia is identical to that of monostotic disease.

TREATMENT

It is impossible to treat all lesions and remove all pigmentations in patients with McCune-Albright syndrome. Surgical management is primarily directed toward alleviating functional disturbances. Sometimes in mild afflictions, cosmetic surgery to improve appearance is effective.

CHERUBISM

CHERUBISM: Autosomal dominant fibro-osseous lesion of the jaws involving more than one quadrant that stabilizes after the growth period, usually leaving some facial deformity and malocclusion.

Cherubism is the name applied to a hereditary form of benign fibro-osseous lesions inherited as an autosomal dominant trait. It has been mapped to the 4p16.3 gene locus, exhibiting a great deal of variability in its expressivity. Found only in the jaws, it mainly involves the mandible in a bilateral symmetrical manner. The maxilla is less commonly involved. The condition's name is derived from the clinical appearance of many of the young patients, particularly those who have involvement of all four quadrants. When expansile lesions are present in the mandible and maxilla, they give the face a "chubby" appearance and often produce some elevation of the floor of the orbits, causing the pupils to be elevated upward. This angelic appearance is reminiscent of the cherub of Romanesque art.

CLINICAL FEATURES

Lesions begin in early childhood as slow-growing expansions of the posterior portions of the mandible or maxilla (Figure 4-12). Expansion is asymptomatic and not



FIGURE 4-12

Cherubism. Facial features resemble a cherub, resulting in part from symmetric bilateral enlargement of the posterior mandible.

limited to the buccal and lingual cortical plates. The ramus may be expanded anteriorly and the other arches superiorly and inferiorly. In addition to obvious facial deformity, concern is directed to interference in mastication and speech development, random alignment of teeth, and resultant severe malocclusion. Lesions continue to enlarge until the patient reaches puberty, at which time the lesions stabilize. In some patients, rib lesions have been found. Eventually the involved bones may undergo some reduction in size. At this time surgical recontouring can make the disfigurement less noticeable.

RADIOGRAPHIC FEATURES

The radiographic appearance is striking, especially during the active growth phases. The overall appearance consists of large areas of radiolucency in the bones that exhibit massive expansion (Figure 4-13). Both erupted and unerupted teeth are randomly distributed within the enlarged arches. Faint radiopacities resembling residual or new bone are sometimes present. As the lesion matures the radiographic appearance gradually changes, with more radiopaque structures becoming evident. After stabilization the involved areas exhibit a "ground glass" radiographic appearance similar to that found in stabilized fibrous dysplasia.

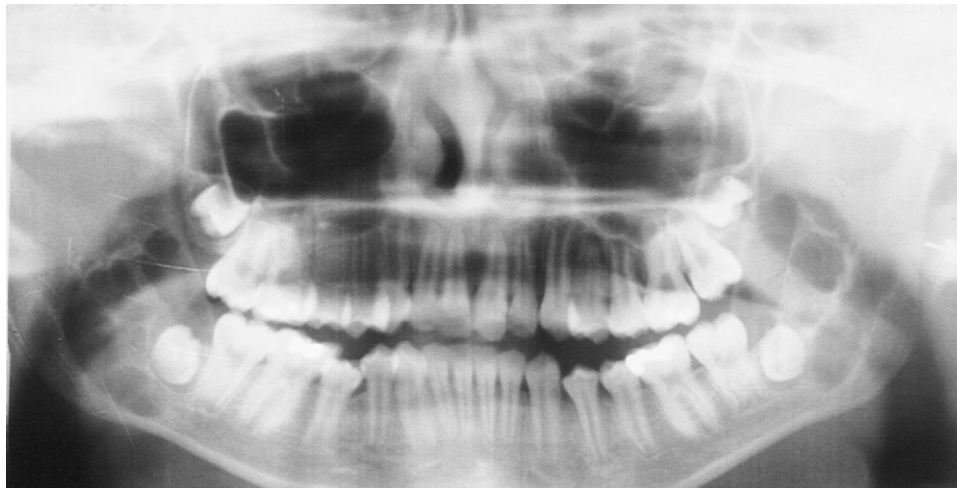
HISTOPATHOLOGY

Tissue findings vary extensively in accordance with the different stages the lesions undergo until stabilization occurs. In the early stages, lesions are composed almost entirely of giant cell tissue in which numerous multinucleated giant cells are present in a background of mononuclear cells (Figure 4-14, A). During this stage the tissues are identical to those of a benign giant cell tumor, a much more serious condition that requires immediate surgical management. As individual lesions mature, the giant cell component is gradually replaced by cellular fibrous tissue in which randomly oriented spicules of metaplastic woven bone develop that resem-

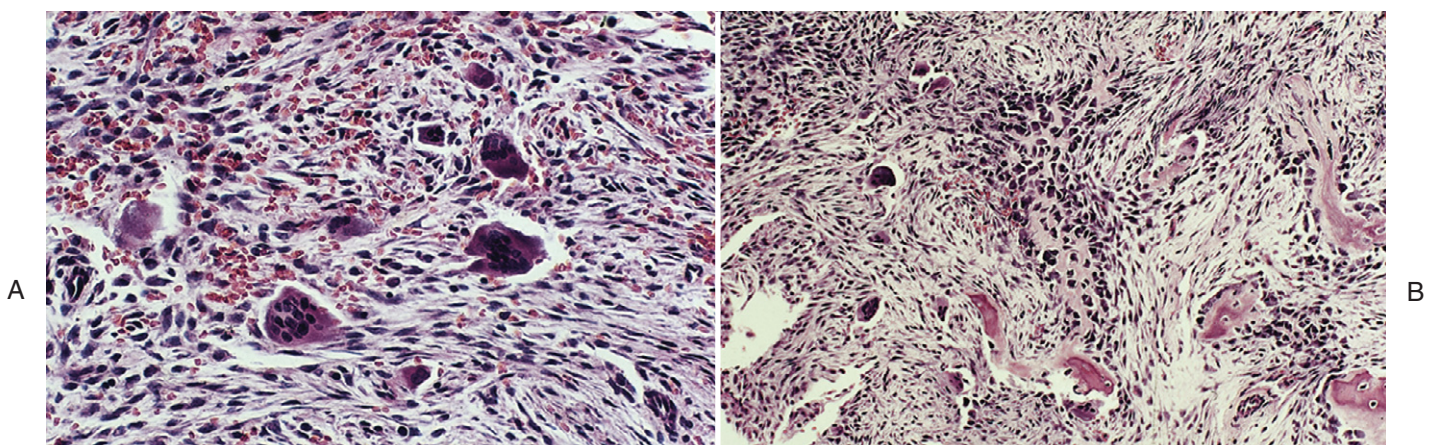
ble those found in fibrous dysplasia (Figure 4-14, B). After lesions become stabilized, the bone dominates the lesion, becoming lamellar and reoriented for structure and function.

TREATMENT

Treatment is directed toward maintaining speech and mastication. Because the condition is self-limiting, with regression and remodeling taking place after puberty, evaluation and cosmetic surgery are delayed until that time. Care must be exercised so that lesions are not mistaken for multiple giant cell tumors and disfiguring surgery unnecessarily performed.

**FIGURE 4-13**

Cherubism. Panoramic radiograph of patient in Figure 4-12 revealing bilateral expansion of the rami and multilocular intraosseous radiolucencies.

**FIGURE 4-14**

Cherubism. **A**, Microscopic appearance of an early-stage lesion containing giant cell tissue with little evidence of fibrous tissue and bone formation. **B**, Mature stage in older patient reveals a reduction in the proportion of giant cell tissue and an increase in fibrous tissue and bone formation.

METABOLIC CONDITIONS

Skeletal bones provide structure and strength to the anatomy and determine overall body size. Of equal importance are their roles as reservoirs for essential metabolic minerals and as envelopes to house the tissues for blood and immune cell production. To carry out these roles, bone cells and their precursors react to the influences of circulating hormones and other body-regulating molecules. Thus bones are particularly sensitive to physiologic and genetic derangement that can result in alterations to their structure and mineral content.

In the past, clinicians lacked insight into the factors governing modulation of bone cells and the pathogenesis of many bone diseases. However, many breakthroughs have recently occurred. Using animal and molecular biology experiments, investigators have isolated key molecules that regulate the differentiation and function of bone cells. It is now known that *Cbfa1/Runx2* and *Osx*, as well as *c-fos* and *ets-1* are transcription factors important in the transition of bone precursor cells to fully functional osteoblasts and osteoclasts, respectively. *TCIRG1*, a subunit of the vacuolar proton pump, and the chloride channel *CLCN7* are particularly critical in osteoclastic function. Osteoprotegerin (OPG), a glycoprotein secreted by osteoblasts, is capable of producing disease states by blocking the differentiation of osteoclast precursors and functioning as a decoy receptor that competes with the osteoclastic receptor activator of nuclear factor-kappa B (RANK) for binding of RANK ligand (RANKL). Competitive disruption of RANKL binding alters the rate of osteoclast differentiation, allowing osteoblastic function to proceed without adequate counterbalancing physiologic bone resorption and resulting in excess bone formation. Alteration in the function of these genes gives rise to many human or animal metabolic bone diseases.

Four metabolic bone diseases that are capable of producing changes in the jaws and other craniofacial bones are discussed in this chapter: (1) Paget disease, (2) hyperparathyroidism, (3) osteopetrosis, and (4) osteogenesis imperfecta.

PAGET DISEASE

PAGET DISEASE: *Uncoordinated increase in the osteoclastic and osteoblastic activity of the bone cells of older adults, producing larger but weaker bones, extensive pain, high levels of serum alkaline phosphatase and urinary hydroxyproline, and an increased tendency to develop malignant bone neoplasms.*

Paget disease (**osteitis deformans**) is an alteration in the histology and morphology of bone. It can be confined to one bone or be distributed in multiple re-

gions throughout the body. It consists of a simultaneous increase in the resorption and apposition mechanisms of bone. Initially the process is dominated by bone resorption, primarily mediated by hyperactivity of osteoclasts. Excessive bone formation follows, with a net increase in volume but a decrease in bone strength. During a period of exacerbation, both osteoclastic resorption and osteoblastic apposition are often found to occur simultaneously on the same side of a section of bone. This uncoordinated function of osteoclastic and osteoblastic activity results in numerous tortuous “cement” or “reversal” lines that give the bone a characteristic mosaic pattern when viewed microscopically.

The pathogenesis of Paget disease of bone is still being unraveled. In Sir James Paget’s original description of the condition, the process was considered an inflammatory process and given the name *osteitis deformans*. That etiology has now been largely discounted, with a coincident drift away from the use of that name. Evidence exists for a genetic predisposition for Paget disease of bone with one such locus identified on chromosome 18q-21-22 (PDB2). Most of the evidence centers on the gene factors capable of altering normal osteoclast behavior. As previously noted, one of the main mechanisms of osteoclast formation and activation involves the OPG, RANK, and RANKL pathways, where binding of RANKL to RANK results in the differentiation of osteoclast precursors. Malfunction of this pathway results in either too much or too little total bone formation. Additionally, interleukin-6 (IL-6) has been found to play a part in patients with Paget disease by increasing the hyperresponsivity of the osteoclast and its precursor cells. Changes in the osteoclast, in turn, produce secondary effects on the other bone cells and the vascularity of the region.

Intranuclear viral inclusion bodies have been found within some of the multiple nuclei of pagetic osteoclasts. Because the inclusion bodies are not present in all nuclei, it has been postulated that they remain in some of the cells’ permanent nuclei and not in transient nuclei. The viruslike structures appear to be paramyxoviral transcripts and antibodies against two of the paramyxoviruses—the measles and canine distemper virus have been found. Inclusion bodies have not been found in the other bone or marrow cells of patients with Paget disease. The basis for the abnormalities detected in Paget disease and the role, if any, that the paramyxoviruses may play is still unclear. It is postulated that the commonly encountered finding of regional, rather than generalized, concentration of patients affected by Paget disease of bone may be explained by these recent findings and the requirement for other concomitant local factors.

CLINICAL FEATURES

Paget disease of bone affects the skeleton in up to 2% to 3% of the population over the age of 60 years and is seldom found in patients younger than 40 years of age. Its exact incidence is difficult to assess, because most cases are asymptomatic and often detected only during a postmortem examination. The prevalence varies throughout the world, being more common in the Western countries. Even within countries, great variability in regional prevalence is seen. Occasionally, families are found that have a much higher incidence than normal for their region, with several members being affected simultaneously.

The disease may be confined to one bone (monostotic) or simultaneous in multiple bones (polyostotic). When multiple bones are involved, most patients develop some degree of incapacity, altered physical appearance, pain, and joint disease. Involvement of the skull is common, resulting in a net increase in head size and shape and in the thickness of the cranial bones. A frequent presenting symptom is a gradual increase in hat size caused by increased cranial circumference. Of more serious concern is the involvement of the base of the skull. In this location, encroachment on the various foramina can result in compression of the spinal cord and cranial nerves and lead to paralysis and loss of hearing and sight.

In the jaws the maxilla is more commonly involved than the mandible. The arch may exhibit complete or partial involvement, giving it either a diffuse enlargement or tumorous appearance (Figure 4-15). Because symptoms are absent, the first sign of involvement may be the gradual appearance of regional or generalized spaces between the teeth. In the edentulous patient a denture may become tight and uncomfortable.

Because all elements of bone turnover are heightened in Paget disease, many bone metabolism markers can be used to make a diagnosis and monitor the disease's progress. The most informative is the assessment of osteoblastic activity as measured by the serum level of **alkaline phosphatase**. Separation of bone-derived alkaline phosphatase from its extraskelatal counterpart is possible but not always necessary in patients with normal liver function and no other disease processes. Normal alkaline phosphatase levels are approximately 63 IU/L, but in Paget disease they may approach 1000 to 5000 IU/L in patients with a polyostotic distribution and 200 to 500 IU/L when a monostotic lesion is present. In monitoring osteoclastic activity, elevated levels of **urinary hydroxyproline** are indicative of increased resorptive activity. The relationship between these two factors is important in the staging and monitoring of the disease. Although considerable calcium loss from bone occurs, serum calcium usually remains within normal levels.

When bones are seriously affected, they often become painful and subject to fracture. Bones that are close to the skin surface, such as the skull, and tibia, will exhibit an elevated surface temperature because of the increase in bone vascularity. Increase in peripheral vascularity, particularly when the vessels are encased within bone, often gives rise to high-output heart failure, a major cause of death in these patients.

The most severe complication of Paget disease is the increased incidence of sarcoma. Sixty percent of patients over the age of 50 with osteosarcoma have an associated polyostotic form of Paget disease. The next most common neoplasm is fibrosarcoma, found in 20% of cases. Benign and malignant giant cell tumors (either solitary or multiple) are also found.

RADIOGRAPHIC FEATURES

A review of radiographic and scintigraphic features are important in the diagnosis of Paget disease. Radiographs provide more detailed information regarding the general architecture and extent of damage, regardless of the degree of disease activity at the time the patient was examined. The radiographic appearance of Paget disease varies extensively. In the early osteolytic stage the bone may exhibit a diffuse radiolucency, but in some late or less active stages a diffuse area of increased bone density is present. The most common radiographic appearance is a combination of radiolucent



FIGURE 4-15
Paget disease. Maxillary enlargement with associated separation of teeth. (Courtesy Dr. Gordon Rick.)

and radiopaque lesions resembling cotton balls in a diffusely defined radiolucent area (Figure 4-16, A). The area is contained within a region of bone that has enlarged and displays thickened but less dense outer cortices. The skull is strikingly involved, with some patients having “cotton ball” cranial cortical plates several centimeters thick. The maxilla and mandible are often greatly enlarged and exhibit loss of the lamina dura. Often teeth in the area exhibit hypercementosis of their roots (Figure 4-16, B).

Scintigraphy does not replace radiographs but is useful in surveying the body for incipient lesions and evaluating the degree of cellular activity of all lesions. The scanning agents are isotopes that are taken up by cells that are actively metabolizing or undergoing rapid mitotic activity. In some cases “hot spots” are found in areas that are normal on radiographs. Although these areas of increased isotope uptake may represent unrelated activities, they often indicate early lesions of Paget disease that have not produced enough osteolysis to be radiographically apparent (Figure 4-17).

HISTOPATHOLOGY

The histopathologic features are essentially the same throughout Paget disease, consisting of an increase in osteoclasts, osteoblasts, and blood vessels and a replacement of the normal dense lamellar bone with a less dense bone having a mosaic pattern (Figure 4-18, A). The phases differ only in the degree of osteoclastic bone resorption and osteoblastic apposition taking place at a given time. During the osteolytic phase, osteoclasts are numerous and large, containing 50 to 100 nuclei. They are present throughout the bone in deep indentations of resorption, with relatively few osteoblasts laying down new woven bone within the region. When the disease is in the **osteosclerotic** phase, osteoblasts predominate and the woven bone matures to dense lamellar bone, with little resorption taking place. The mixed phase consists of zones in which each end of the spectrum is present simultaneously. The mosaic pattern is a prominent feature of the residual matured lamellar bone that is found in the mixed and osteosclerotic phases of the disease, with the lines



FIGURE 4-16

Paget disease. **A**, Mandible, maxilla, and part of cranium exhibiting a mottled mixture of radiopaque and radiolucent bone formation (“cotton ball” appearance). **B**, Periapical radiograph of teeth exhibiting hypercementosis and loss of lamina dura.

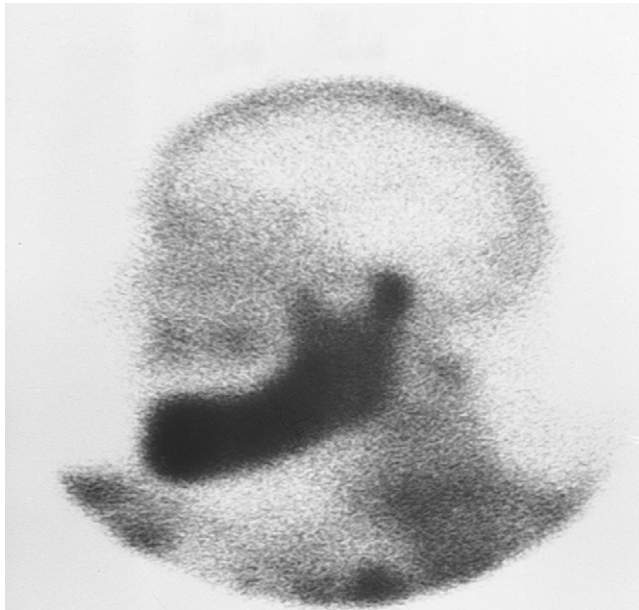


FIGURE 4-17
Paget disease. Scintigraphy demonstrates notable increases in uptake of isotope (“hot spots”) in mandible, vertebrae, and clavicle of patient with active disease.

reflecting the many reversals in bone cell activity (Figure 4-18, B).

TREATMENT

Treatment is not routinely administered to patients with Paget disease, because many are elderly and asymptomatic. Those who become immobilized or have severe pain, preexisting cardiac failure, renal calculi, or severe neurologic deficits are considered for treatment. In the past the most effective therapeutic agents have been calcitonin and diphosphonates, such as disodium etidronate. It is now found that disodium etidronate has little place in the modern management of Paget disease. Newer bisphosphonates such as alendronate and risedronate provide significant therapeutic advantages over etidronate, both in the extent of reduction in bone-specific alkaline phosphatase, total serum alkaline phosphatase, or both and in the duration of remission. These compounds inhibit bone resorption through their inhibitory effect on osteoclasts. This provides the bone-forming cells a chance to keep pace with bone resorption and produce an environment approaching that of normal bone.

Treatment does not stop the process, but it does considerably slow it and produce stronger, less fragile

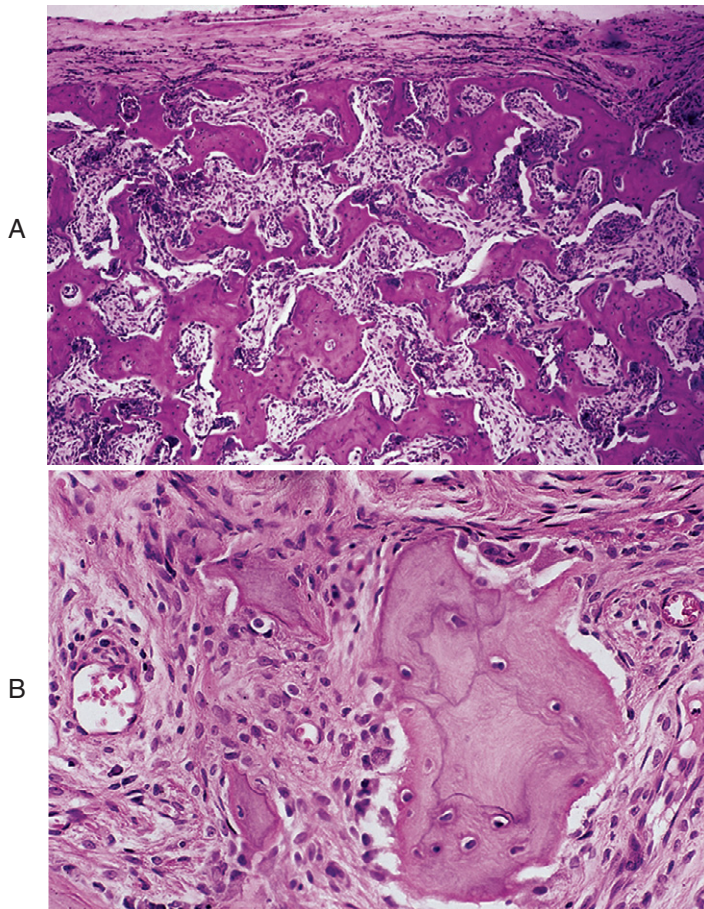
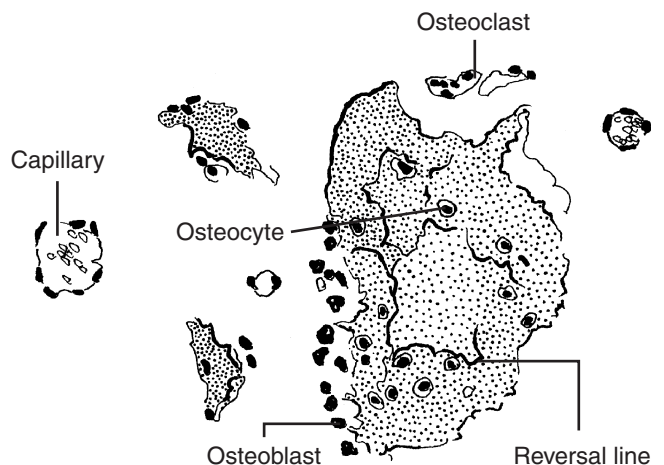


FIGURE 4-18

Paget disease. **A**, Replacement of normal cortical lamellar bone by a thickened layer of irregular bone fragments surrounded by fibrous tissue with increased numbers of osteoblastic and osteoclastic cells. **B**, High-power photomicrograph of fragment of pagetoid bone exhibiting reversal lines caused by multiple alterations of osteoblastic and osteoclastic activity, resulting in a characteristic mosaic pattern.



bone. Surgery of the abnormally formed bone is to be avoided as much as possible. The osteolytic bone is prone to hemorrhage, and the osteosclerotic bone is prone to an osteomyelitis that is difficult to manage. Surgery is used only to relieve severe pain caused by pressure on nerves and the spinal cord and for open reduction procedures during fracture fixation.

HYPERPARATHYROIDISM

HYPERPARATHYROIDISM: *Loss of bone mineralization (osteoporosis) because of increased PTH secretion (primary) or increased demand for serum calcium (secondary), resulting in multiple systemic complications, loss of alveolar bone architecture, and occasionally giant cell tumor ("brown tumor").*

Hyperparathyroidism may be primarily caused by excessive secretion of parathyroid hormone (PTH) or secondarily by kidney disease. In both, resultant hypercalcemia and hypophosphatemia can give rise to associated disturbances in ion metabolism, depletion of bone minerals, kidney stones, gastrointestinal disorders, and muscle weakness. The hypersecretion in primary hyperparathyroidism is most commonly the result of the presence of one or more adenomas of the parathyroid gland. If the adenomas are discovered early and surgically removed, the patient quickly reverts to normal. However, not all excess parathormone secretion is the result of adenomas. In some patients the gland may be reacting secondarily to other alterations in the body, with the increased secretion part of a compensatory mechanism. This form of the disease is termed *secondary hyperparathyroidism*. The most common alteration is renal disease in which chronic loss of circulating phosphate ion is the result of damage to the kidneys' distal tubules. The depleted serum phosphate ion causes a constant demand for calcium to maintain the electrolyte balance. Increased amounts of PTH are required to liberate calcium from the bone reservoir through osteolysis. Less commonly, patients may have an idiopathic hyperplasia of all four parathyroid glands. This form of the disease is more common when the condition is familial. Regardless of the cause, the resulting manifestations of hyperparathyroidism are the same in all patients.

CLINICAL FEATURES

In patients over 60 years of age, some degree of hyperparathyroidism is found in 1:500 women and 1:1000 men. Most patients are asymptomatic, and treatment is unnecessary. They are monitored for kidney stones and for the extent of their osteolysis. Hypercalcemia is the most common manifestation of hyperparathyroidism and is diagnosed when serum calcium is above the normal range of 8.6 to 10.4 mg/100 ml. A lowered serum

phosphate level also is helpful in confirming the diagnosis. Levels of urinary phosphate may be elevated. In most cases the serum alkaline phosphatase and urinary hydroxyproline are not elevated unless the condition is severe. This finding indicates rapid bone turnover with a net loss of bone structure that should be visible on radiographs. Because many causes other than excessive PTH secretion can lead to hypercalcemia, immunoassays for PTH are often performed to confirm the diagnosis.

RADIOGRAPHIC FEATURES

Bone changes consist of either a subtle generalized reduced bone density (osteoporosis) or mottled areas of radiolucency with thinning of the cortical plates and the medullary bone (osteitis fibrosa cystica). In the mandible and maxilla, the normal trabecular pattern may be lost, and some lack of distinctness of the lamina dura occurs in the late stages of chronic or severe disease (Figure 4-19). Occasionally a large destructive radiolucency may be present, indicative of a giant cell tumor of hyperthyroidism ("brown tumor"). These lesions are reversible if the condition predisposing the patient to hyperparathyroidism can be corrected.

HISTOPATHOLOGY

Microscopic findings are generally subtle and nonspecific, consisting of increased osteoclastic activity, thinning of the trabecular bone, and wide zones of osteoid rimmed with activated osteoblasts. Some replacement of marrow with loose cellular connective tissue may occur. On rare occasions, destructive lesions that are histologically identical to other forms of giant cell bone lesions may be present.



FIGURE 4-19

Hyperparathyroidism. Radiograph of mandibular alveolar process demonstrating generalized lack of bone density, indistinct trabecular pattern, and loss of the normally distinct lamina dura surrounding roots of the teeth.

TREATMENT

The treatment of hyperparathyroidism depends on the cause. Surgery can correct excessive PTH secretions when they are the result of hyperplasia or neoplasia of the parathyroid glands. Medical management is usually preferred in milder forms of the disease if the patient is over 50 years old and progressive bone loss has not occurred. Patients who are being medically treated need to be carefully monitored, because mineral and vitamin supplements may trigger other, more severe problems. Newer therapeutic options include less use of vitamin D analogues, calcimimetics, and bisphosphonates. Calcitriol and hormone replacement therapies have been shown to maintain bone mineral density in patients with end-stage renal disease. Bisphosphonate therapy may be appropriate for those patients at risk for bone fractures.

OSTEOPETROSIS

OSTEOPETROSIS: *Generalized hereditary condition consisting of excessive bone mineralization, resulting in altered stature, frequent fractures, lack of bone marrow hematopoietic function, and a tendency for severe osteomyelitis of the jaws.*

Osteopetrosis is a generalized hereditary condition in which the bones become substantially denser than normal. Other hormonal, metabolic, dietary, or hereditary disorders can also produce osteopetrosis. The most common forms are hereditary, consisting of a benign type of osteopetrosis that is autosomal dominant with a gene locus at 1p21 and a malignant autosomal recessive osteopetrosis with gene locations at 16p13 and 11q13.4-q13.5.

As more information regarding bone function is gained, it appears that the pathogenesis of osteopetrosis is due to a reduction in osteoclastic activity. Using animal experiments, it has been found that malfunction of the previously mentioned OPG, RANK, and RANKL pathway results in a reduction in osteoclastic differentiation, allowing osteoblastic function and bone formation to proceed unabated.

CLINICAL FEATURES

The most serious clinical features of osteopetrosis are lack of resorption of calcified cartilage during endochondral growth, reduced marrow space for red and white blood cell development, and overly deposited and mineralized bones. The defects result in patients of short stature who are highly susceptible to infection and hemorrhage and who are reluctant to participate in vigorous activities because of the high frequency of bone fracture.

Patients with the more severe form of osteopetrosis have symptoms that begin in infancy with breathing

and hearing difficulties because of oversized facial and mastoid bones. These are followed by functional defects in the ocular and trigeminal nerves as they become compressed by sclerosis of the foramina of the base of the skull.

Eventually the patients develop an enlarged cranium with prominent frontal bossing. The commonly occurring delay in dental development and eruption of teeth can sometimes be restored in a child with congenital osteopetrosis with the use of a bone marrow transplantation that induces normal osteoclast function. The long bones are shortened and extremely fragile, and they exhibit replacement of marrow with dense bone. This results in depletion of platelets, leukocytes, and erythrocytes, which produces a tendency for spontaneous hematomas, multiple infections, and anemia. Patients with severe osteopetrosis usually die from complications of marrow depletion before they reach 10 years of age.

In the more benign forms, reduced stature occurs less commonly and nerve deficits are less severe. Teeth erupt but have a tendency for ankylosis. Routine extraction and periapical infection from advanced caries often result in a persistent osteomyelitis caused by dense avascular bone and limited connective tissue unable to initiate an adequate healing response.

RADIOGRAPHIC FEATURES

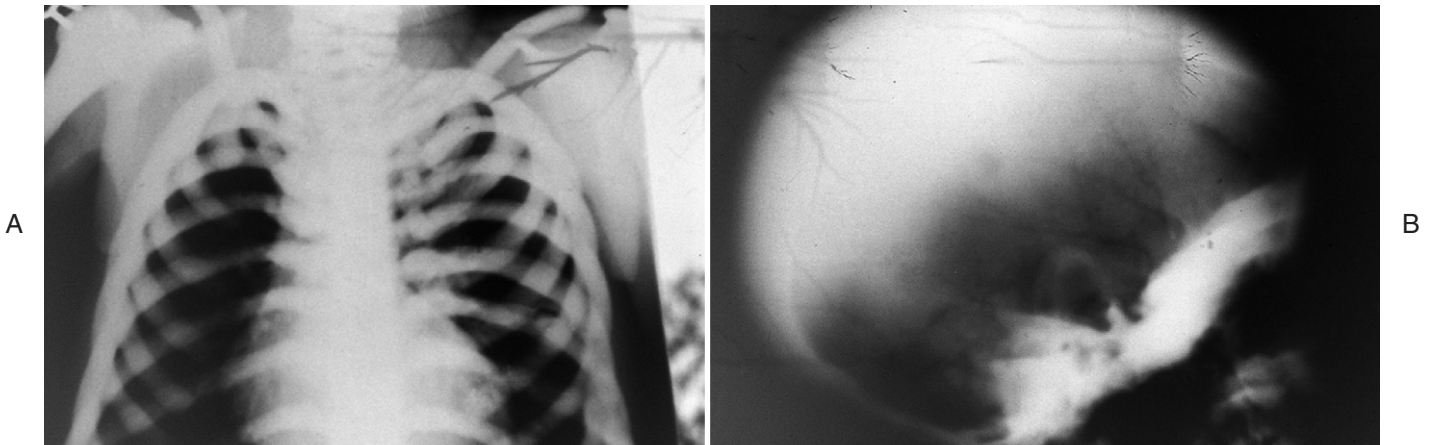
Radiographs exhibit a generalized increase in bone density with obliteration of normal internal architecture. It is particularly severe in the enchondral areas of long bone. The cartilaginous portion of the ribs also exhibits an uncharacteristic increase in opacity (Figure 4-20, A). The cranial plates are thickened, and the base is affected to a greater degree than the other bones (Figure 4-20, B). Sinus cavities are greatly reduced in size. Fracture of the long bones is common. Embedded or unerupted teeth are common in the severe forms of the disease (Figure 4-21).

HISTOPATHOLOGY

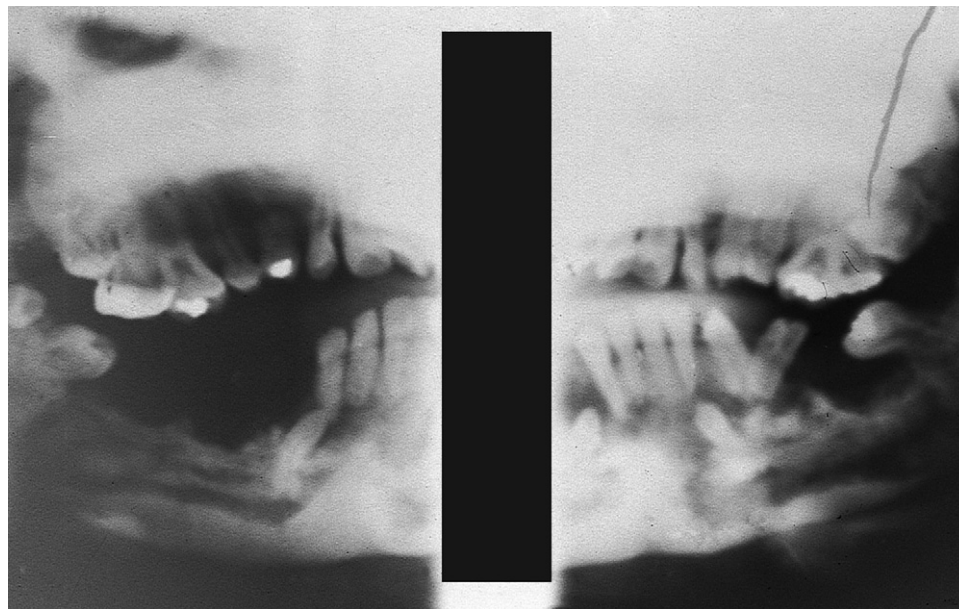
The bone is dense and sclerotic, with most of the marrow spaces replaced with bone or fibrous tissue. In some forms a normal number of osteoclasts are present but do not display a ruffled border and clear zone that are present in normal functioning cells during resorption. In other forms of the disease the number of osteoclasts is greatly reduced. The bone is somewhat avascular; in some cases, islands of calcified cartilage are found that should normally be resorbed during development.

TREATMENT

Treatment depends on the form of the condition. Transplantation of allogenic bone marrow has been helpful in relieving some of the hematologic and neurologic

**FIGURE 4-20**

Osteopetrosis. **A,** Ribs, humerus, and clavicles exhibit increased bone density. **B,** Increase in bone density of cranial and base-of-skull bones.

**FIGURE 4-21**

Osteopetrosis. Panoramic radiograph demonstrating unerupted teeth and areas of increased bone density of the mandible and maxilla.

problems in some forms of the disease and has helped restore a population of competent osteoclasts. In other forms, marrow transplants have been of little use. Oral calcitriol combined with a calcium-deficient diet has provided some improvement. In milder forms, osteomyelitis of the jaws has been successfully treated with hyperbaric oxygen. In those severely afflicted, resection of portions of the mandible is usually necessary.

OSTEOGENESIS IMPERFECTA

OSTEOGENESIS IMPERFECTA: A spectrum of diseases of bone caused by a basic alteration in the formation of bone connective tissue matrix, resulting in an inability of the matrix to fully mineralize, a tendency for multiple broken bones, blue sclera of the eyes, and associated dentinogenesis imperfecta.

Osteogenesis imperfecta (OI) is a genetically determined disorder of connective tissue characterized by

bone fragility. The disease encompasses a phenotypically and genotypically heterogeneous group of inherited disorders that result from mutations in the genes that code for type I procollagen. Molecular genetic studies have identified more than 150 mutations of the COL1A1 gene on chromosome 17 and COL1A2 gene on chromosome 7. The disorder is manifested in tissues in which the principal matrix protein is type I collagen. These are mainly bone, ligaments, sclera, and dentin.

In contrast to osteopetrosis, OI is characterized by defective matrix formation and a lack of mineralization rather than hypermineralization. The net result is similar to osteopetrosis in that the patient has bone fragility, multiple fractures, and hearing defects. Of importance is the close association of OI with dentinogenesis imperfecta. The previous categorizations of “OI congenital” and “OI tarda,” indicating the age when fractures begin and the disease’s severity, are no longer used. In 1988 a classification of OI was developed based on specific phenotypes, biochemical data, and hereditary patterns. It classifies OI into four types according to onset and lethality: (1) *neonatal lethal*; (2) *severe nonlethal*; (3) *moderate and deforming*; and (4) *mild nondeforming*. Many patients share clinical features with other hereditary connective tissue diseases, such as Ehlers-Danlos syndrome and Marfan syndrome.

CLINICAL FEATURES

The neonatal lethal form of OI occurs in 10% of cases, with patients suffering multiple fractures during gestation and delivery. Most die within weeks if they survive birth. The severe nonlethal form occurs in 20% of patients; they also have multiple fractures at birth. The



FIGURE 4-22
Osteogenesis imperfecta. Characteristic blue sclera of the moderate, deforming type of the disease.

patient has fragility and generalized deformity of all bones, blue sclera of the eyes, and dentinogenesis imperfecta. Patients are confined to a wheelchair. Patients with the moderate and deforming type are less severely affected than the other two, but have a high incidence of blue sclera (Figure 4-22) and dentinogenesis imperfecta. The mild nondeforming type affects 60% of patients. Little evidence of the condition is present at birth, but the ease of bone fractures appears as the child begins to walk. The incidence of fractures declines at puberty. All patients have some degree of blue sclera, but only 25% will have dentinogenesis imperfecta. Some joint laxity is present, and 70% will have hearing impairment.

RADIOGRAPHIC FEATURES

Radiographs exhibit shortened, deformed extremities with large areas of cystlike radiolucencies. The midshaft areas are narrowed with bulbous metaphyseal and epiphyseal zones. Multiple fractures and healed fractures are apparent. Nearly all forms exhibit some spinal scoliosis. The teeth exhibit the usual changes of dentinogenesis imperfecta with bulbous crowns, obliteration of the pulpal chambers, and shortened roots. Unilocular radiolucencies that occupy both sides of the mandible have been found. They are similar surgically and microscopically to traumatic bone cysts.

HISTOPATHOLOGY

The bones of patients with severe forms of OI have markedly thinned cortices composed of immature woven bone. The trabeculae are short, thin, widely spaced, and disorganized. Bones display an increased number of osteoblasts, osteoclasts, and osteocytes, as well as decreased mineral content.

TREATMENT

The goals of treatment of OI are to maximize function, minimize deformity and disability, and maintain comfort. Treatment is tailored to the severity of the disease and the age of the patient. Orthopedic treatment is usually nonsurgical, with the management goals aimed at preventing and treating fractures and enhancing locomotion. Surgical intervention is indicated for recurrent fractures or deformity that impairs function.

BENIGN TUMORS

Other than odontogenic tumors, the number of true neoplasms arising within the jaws is small. Although some are locally destructive, most of the common tumorous lesions such as tori, exostoses, and peripheral and even most central giant cell lesions are not true neoplasms. Other neoplasms occurring in and around

the mandible and maxilla are derived from tissue that gives rise to blood vessels and lymphatics, nerves and lymphocytes, and myelogenous and erythrocyte series of cells; they are discussed in Chapters 9 and 12.

TORUS, EXOSTOSIS, AND OSTEOMA

TORUS: *Rounded, smooth-surfaced, nonneoplastic growth of nodular dense bone found on the midline of the palate and lingual surfaces of the mandible.*

A torus commonly occurs in two specific intraoral locations: (1) on the midline of the hard palate, termed *torus palatinus*, and (2) on the lingual of the mandible in the cuspid and premolar region, termed *torus mandibularis*. Histologically identical lesions occurring on the alveolar bone of the mandible and maxilla in other regions of the gingiva are termed *exostoses*. Similar lesions arising on the periosteal surfaces, but not in the previously mentioned locations, are termed *osteomas*. Whereas tori and exostoses are thought to be reactions to bone stresses, the osteomas are considered benign neoplasms.

CLINICAL FEATURES

Torus Palatinus

TORUS PALATINUS: *An exophytic nodular growth of dense cortical bone located on the midline of the hard palate.*

Torus palatinus is found on the midpalate of over 20% of adults. It is not present in young patients, developing only after puberty in susceptible individuals. Once begun, lesions usually grow slowly over the patient's entire life. Growths commonly consist of four

evenly spaced lobes composed of dense bone with a thin layer of mucosa tightly stretched over the surface (Figure 4-23, A). Lesions can grow large, sometimes becoming pedunculated. Larger tori interfere with speech, placement of prosthetic appliances, and oral hygiene maintenance and may develop nonhealing ulcers (Figure 4-23, B) that progress to chronic osteomyelitis.

Torus Mandibularis

TORUS MANDIBULARIS: *An exophytic nodular growth of dense cortical bone located in the cuspid and premolar area of the lingual mandible.*

Torus mandibularis is commonly found bilaterally in the cuspid area of the lingual mandible (Figure 4-24). In some racial groups such as northern native peoples it occurs in over 30% of adults. The tori are slow growing, usually multiple lobed, and may become very large. Larger growths may interfere with tongue movement, oral hygiene maintenance, and the ability to wear an intraoral prosthesis. They are easily lacerated and slow to heal.

Exostosis

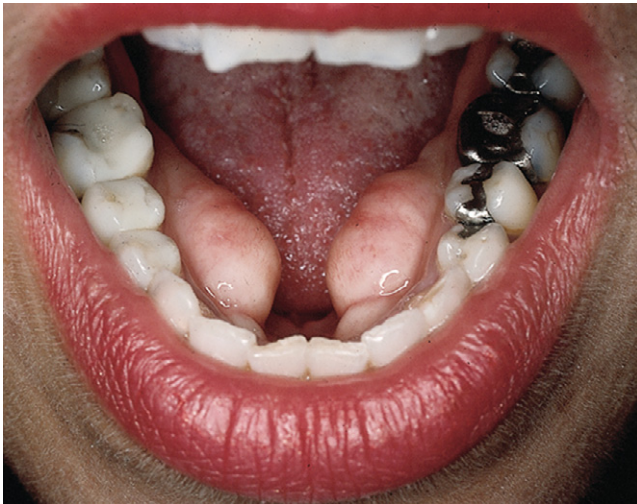
EXOSTOSIS: *An exophytic nodular growth of dense cortical bone commonly located on maxillary or mandibular buccal alveolar bone, usually in the bicuspid and molar area.*

Exostoses are found randomly in adult patients, usually occurring on the attached gingiva over the apices of teeth. They most commonly appear on the buccal plate over the bicuspids (Figure 4-25) as multiple rounded or oval nodules of dense bone (Figure 4-26). They are of



FIGURE 4-23

Torus palatinus. **A,** Typical presentation as four lobes of dense bone located in the midline of the hard palate. **B,** A common complication of unremoved lesions is chronic ulceration that often leads to focal osteomyelitis.

**FIGURE 4-24**

Torus mandibularis. Unusually large lesions located on the lingual cortical bone in the cuspid and premolar area of the mandible.

**FIGURE 4-25**

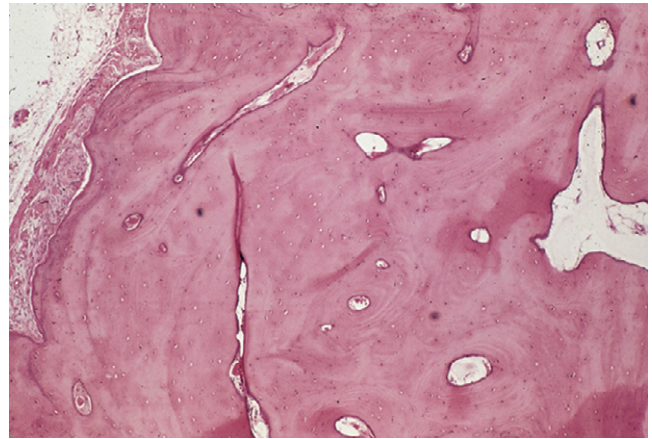
Exostoses. Lesions commonly occur on the buccal cortical bone in premolar and molar areas.

little consequence to the patient unless they are cosmetically unacceptable or interfere with the placement of a prosthesis.

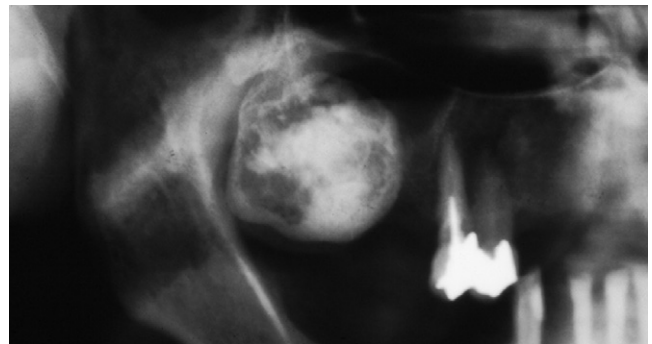
Osteoma

OSTEOMA: An exophytic nodular growth of dense cortical bone on or within the mandible or maxilla in locations other than those occupied by tori or exostoses.

Osteomas are found at nearly any age and may be solitary (Figure 4-27) or multiple. They may be located either superficially or intraosseously on any bone of the cranium or face or within the sinus cavities. When multiple, they are often associated with **Gardner syndrome**,

**FIGURE 4-26**

Exostoses. Photomicrograph of periphery of bone nodule consisting of dense cortical bone exhibiting sclerosis, loss of marrow spaces, and increased periosteal cellularity.

**FIGURE 4-27**

Osteoma. Solitary lesion of posterior maxilla.

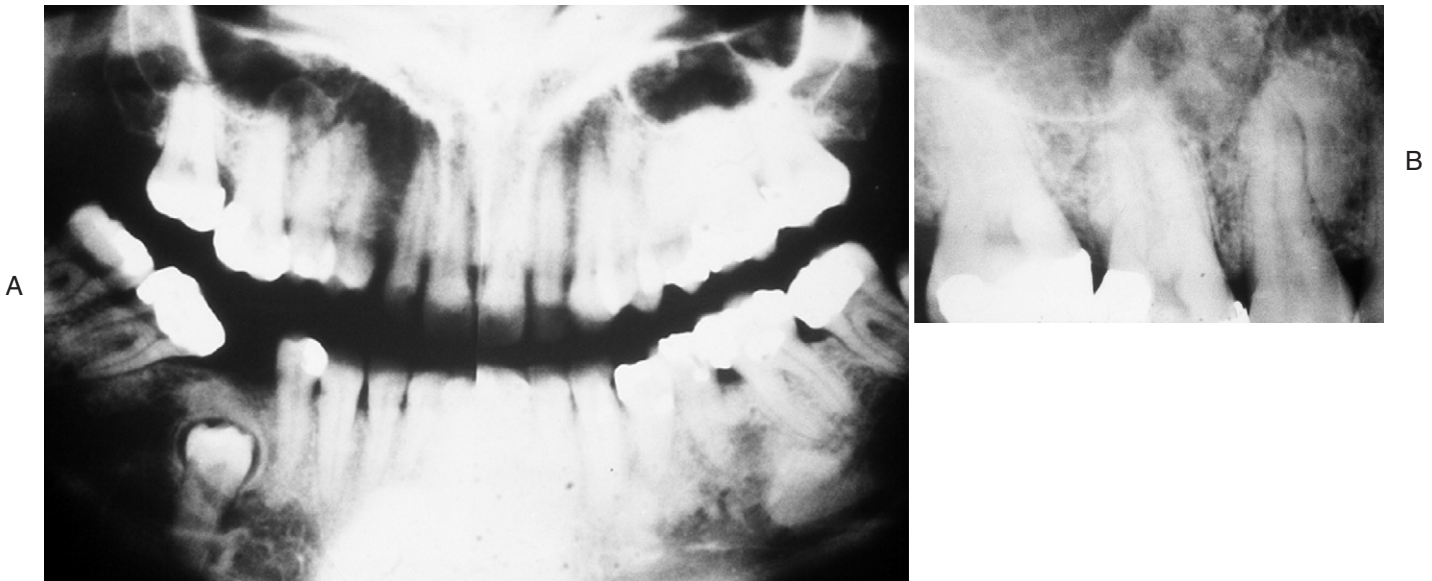
a hereditary condition with an autosomal dominant pattern and a gene locus at 5q21-q22 (Figure 4-28). The syndrome consists of multiple intestinal polyps with malignant potential, unerupted normal and supernumerary teeth, and cysts and fibromas of the skin.

HISTOPATHOLOGY

Each of the lesions is composed of dense cortical bone with a lamellar pattern. The cortical bone is sclerotic and relatively avascular. The medullary bone is denser than normal with reduced marrow spaces. The periosteal layer is often more active in osteoma than in tori or exostoses.

TREATMENT

Lesions are only treated if the patient encounters problems or a prosthetic appliance is necessary. Treatment of tori and exostoses consists of surgically reducing the lesions to the level of the surrounding bone. Surface osteomas are similarly treated but may recur. Removal of intraosseous lesions is only pursued if embedded teeth

**FIGURE 4-28**

Multiple osteomas of Gardner syndrome. **A**, Panoramic radiograph of mixed intraosseous and extraosseous osteomas and associated unerupted teeth. **B**, Periapical radiograph of intraosseous and superimposed extraosseous osteomas.

are to be removed or brought into positions to allow them to erupt fully.

OSTEOID OSTEOMA AND OSTEOLASTOMA

OSTEOID OSTEOMA AND OSTEOLASTOMA:

Benign intraosseous lesions with similar clinical, radiographic, and histopathologic features consisting of well-demarcated, rounded intraosseous swellings, each with an active cellular central nidus surrounded by a wide zone of osteoid, with pain upon palpation.

CLINICAL FEATURES

Osteoid osteoma and osteoblastoma share many common clinical and histological features with each other and with cementoblastoma. All produce swelling and pain (particularly when pressure is applied), and all occur in young patients. A similar histologic pattern is common to all lesions, consisting of a central nidus of increased vascularity with extremely active osteoblasts and osteoclasts surrounded by cellular bone that contains a wide zone of osteoid. They differ in that osteoid osteoma is small (0.5 to 2.0 cm), and osteoblastomas and cementoblastomas are large (>2.0 cm).

Cementoblastoma also differs, because it surrounds and is in continuity with the root cementum of a molar. The three lesions are considered variations of the same process.

**FIGURE 4-29**

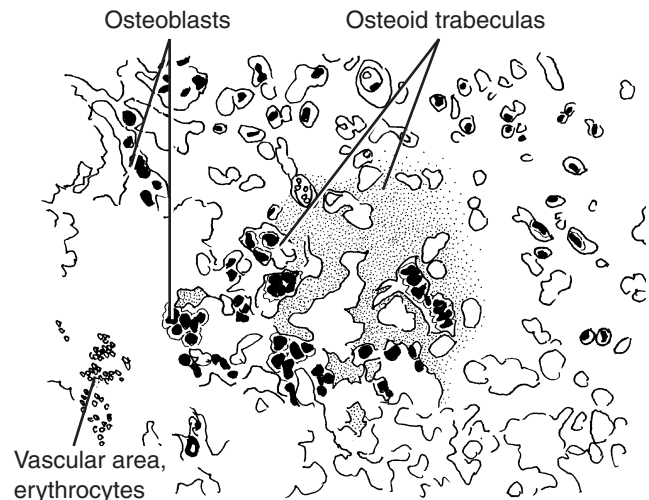
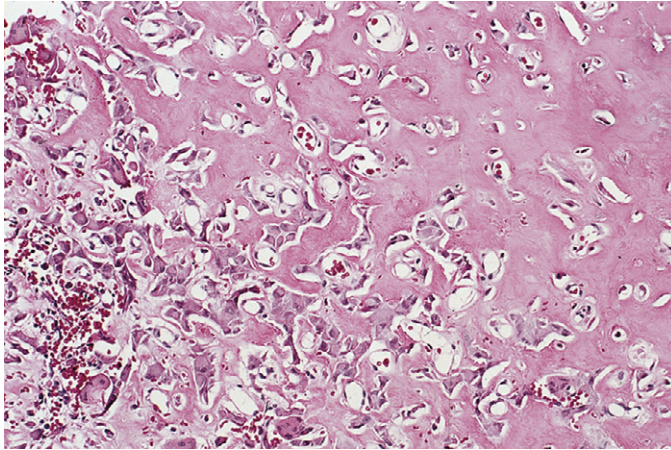
Osteoblastoma. Panoramic radiograph of a well-demarcated expansile lesion exhibiting faint central radiolucency.

RADIOGRAPHIC FEATURES

The radiographic features of osteoid osteoma and osteoblastoma are distinctive and pathognomonic. They are rounded, with a well-defined central radiolucency (nidus) surrounded by a zone of increased radiopacity (Figure 4-29).

HISTOPATHOLOGY

All lesions pass through several phases. Initially a small focus of active osteoblasts is followed by a period in which wide zones of osteoid are deposited. In the matured stage,

**FIGURE 4-30**

Osteoblastoma. Microscopic features display characteristic wide peripheral zone of cellular osteoid and bone (*right*) and central nidus of vascular connective tissue containing increased numbers of osteoblasts and osteoclasts and reduced bone formation (*left*).

the osteoid becomes well calcified, creating an atypical form of bone. The center usually remains vascular with increased numbers of plump osteoblasts and large osteoclasts (Figure 4-30). The density and size of the cellular component is often of concern and can be confused as a sign of malignancy.

TREATMENT

Treatment of osteoid osteoma is directed at removal of the radiolucent nidus or active cellular area of the lesion. In some this has been successfully accomplished with curettage, but others require block resection. Osteoblastoma often requires a large surgical en bloc specimen because of the size of the lesion.

CEMENTO-OSSIFYING FIBROMA

CEMENTO-OSSIFYING FIBROMA: A well-demarcated, encapsulated, expansile intraosseous lesion of the jaws composed of cellular fibrous tissue containing spherical calcifications and irregular, randomly oriented bony structures.

The cemento-ossifying fibroma (COF) is also widely known as *ossifying fibroma*, a term applied to lesions of extragnathic bones that do not contain the spherical calcification commonly found in the jaw lesions. Although jaw and nonjaw lesions may or may not contain the spherical calcifications thought by some to be an aberrant form of cementum (cementicles), the incidence is far higher in the mandible and maxilla. In some jaw lesions the calcifications are exclusively cementicles, and the lesions are termed *cementifying fibroma*. When lesions containing the spherical calcifications occur in the sinonasal and orbital

bones in young patients, they have been termed *psammomatoid juvenile ossifying fibroma*. Lesions of the maxilla and mandible with trabecular bone as the main histologic feature have been referred to as *trabecular juvenile ossifying fibroma*. Studies have shown that the biologic behavior of all histologic variants is similar, causing expansion of the cortical plates, replacement of normal bone with neoplastic cellular fibrous tissue, and formation of spherical calcifications and irregular, randomly oriented bony structures. The histologic features of many COFs closely resemble those of fibrous dysplasia. It is separated from fibrous dysplasia primarily by its clinical and radiographic features and the finding that the neoplastic tissue does not blend with the surrounding bone but is sharply demarcated from it by a thin zone of fibrous tissue. A faster growing and more destructive variant of COF sometimes occurs in patients under age 15 and is termed *juvenile, or aggressive, ossifying fibroma*.

CLINICAL FEATURES

COF is most often located in the mandible posterior to the canines and only occasionally in the maxilla and other locations. It occurs twice as often in women and primarily in the 20- to 30-year age group. The lesion is usually painless and grows slowly, exhibiting marked buccal and lingual bony expansion (Figure 4-31).

RADIOGRAPHIC FEATURES

The radiographic appearance is of utmost importance in the diagnosis of COF, because it is often needed to separate it from other fibro-osseous lesions. The lesions may be either unilocular or multilocular. In the early stages the lesions are small and usually completely radiolucent.

As they enlarge, increased amounts of irregularly shaped radiopacities appear within the radiolucent area. In the later, more mature stage, the radiopaque structures enlarge and coalesce, often forming a nearly radiopaque lesion with a thin rim of radiolucency separating it from the surrounding normal bone. Root resorption and displacement of teeth are frequent findings (Figure 4-32).

HISTOPATHOLOGY

The microscopic findings mirror the radiographic findings. The more radiolucent lesions are composed of cellular fibrous connective tissue, frequently in a whorled pattern. Spherical amorphous calcifications of various

sizes (cementicles) are often present and randomly distributed (Figure 4-33, A). Irregularly shaped calcified structures containing osteocytes and a wide zone of osteoid and osteoblasts are frequently intermingled. A thin outer zone of fibrous connective tissue is usually present, separating the fibroosseous tissue from the surrounding normal bone (Figure 4-33, B).

TREATMENT

Treatment is surgical removal with the extent depending on the size and location of the individual lesion and the extent of any capsule formation. Some lesions have successfully been removed with curettage and local excision, whereas others required block resection. In the more aggressive lesions, multiple recurrences are common.

GIANT CELL LESIONS

Many lesions of the mandible and maxilla contain giant cell tissue. They include peripheral giant cell granuloma (PGCG), central giant cell granuloma (CGCG) and tumor, aneurysmal bone cyst (ABC), “brown tumor” of hyperparathyroidism, and early stage cherubism (Box 4-2). In all of these lesions the giant cell tissue has the same histopathologic composition— accumulations of multinucleated giant cells in a background of mononuclear fibrohistiocytic cells, plump fibroblasts, and extravasated red blood cells (Figure 4-34).

The histologic features of each of these lesions are markedly similar, although they vary substantially in their clinical behavior. They are designated as separate



FIGURE 4-31
Cemento-ossifying fibroma. Expansile lesion of right mandible.

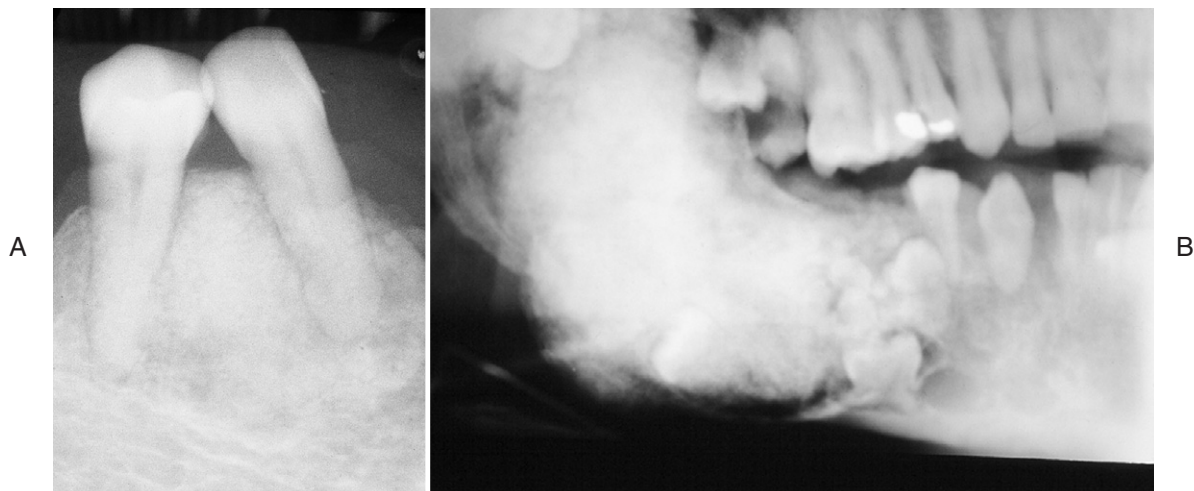


FIGURE 4-32
Cemento-ossifying fibroma. **A**, Periapical radiograph of patient in Figure 4-31 exhibiting a unilocular radiopaque lesion with a well-demarcated periphery and displacement of roots of involved teeth. **B**, Panoramic radiograph of large expansile radiopaque lesion of posterior mandible revealing molar impaction, root resorption, and displacement of posterior teeth.

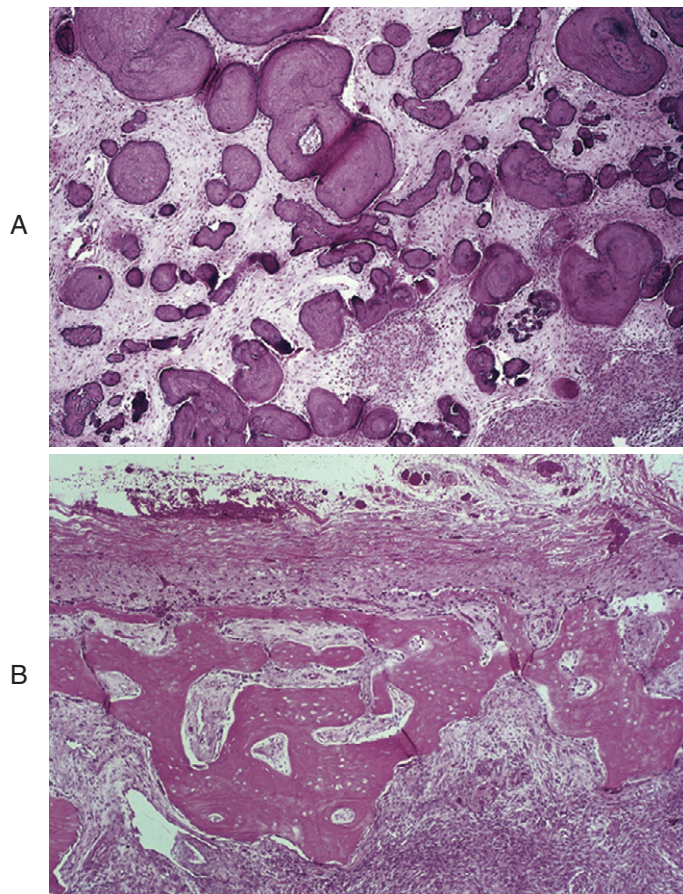


FIGURE 4-33
Cemento-ossifying fibroma. Photomicrographs of characteristic cellular fibrous connective tissue containing coalesced calcified structures **(A)** and periphery showing a well-formed fibrous capsule separating lesional tissue from the surrounding normal tissue (*top*) **(B)**.

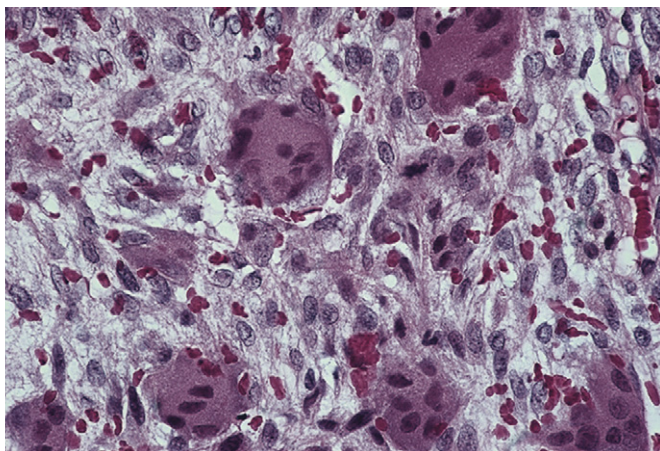


FIGURE 4-34
Giant cell tissue. Photomicrograph of basic histopathologic features of all giant cell lesions—large multinucleated cells surrounded by mononuclear fibrohistiocytic cells, matured fibroblasts, and extravasated red blood cells. Individual lesions will vary in the proportion of each of the components.

entities based on a combination of their microscopic features, location, and associated clinical features.

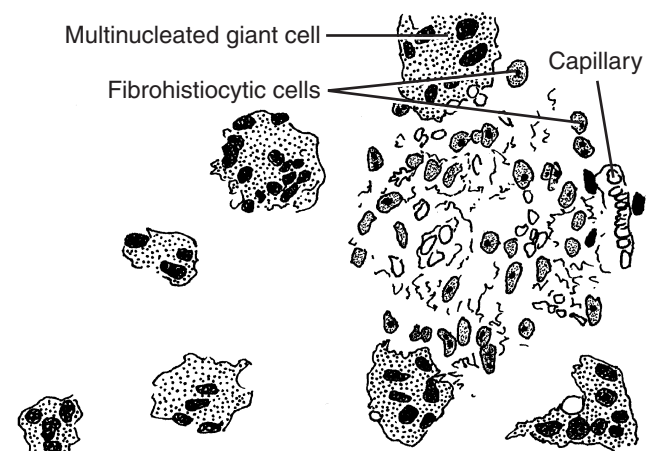
Controversy still exists over whether the central giant cell lesion that occurs in the jaws is a true neoplasm, identical to those that occur in the long bones. Many believe that intraosseous jaw lesions are not as aggressive as their long bone counterparts and prefer to identify them as CGCGs. The majority of investigators now acknowledge that although most are not aggressive, lesions do occasionally occur in the jaws that are identical to the aggressive, high-grade lesions that are sometimes found in the extremities; when this type occurs, the lesion should be referred to as *central giant cell tumor*. The occurrence of a true undisputed neoplastic giant cell lesion of the jaws has been documented in the reported case of a young patient with a malignant central giant cell lesion of the mandible who died with radiographic evidence of pulmonary metastasis.

PGCG, CGCG, and ABC are discussed in this chapter; the other previously mentioned lesions are discussed elsewhere.

BOX 4-2

Lesions of the Jaws Containing Giant Cell Tissue

Central giant cell granuloma
Peripheral giant cell granuloma
Cherubism
Aneurysmal bone cyst
“Brown tumor” of hyperparathyroidism



Peripheral Giant Cell Granuloma

PERIPHERAL GIANT CELL GRANULOMA: An extraosseous nodule composed of a proliferation of mononuclear and multinucleated giant cells with an associated prominent vascularity found on the gingiva or alveolar ridge.

CLINICAL FEATURES

The PGCG is the most common giant cell lesion occurring in the jaws, arising from the connective tissue of the periosteum and periodontal membrane. It occurs throughout life, with peaks in the incidence during the mixed dentition years and the 30- to 40-year-old age group. It is more common among women. PGCG most often appears as a



FIGURE 4-35
Peripheral giant cell granuloma. Lesion of mandibular gingiva exhibiting a focal area of ulceration on its upper surface.

sessile focal purplish nodule on the gingiva. Lesions can become large, some attaining 2 cm in size. They are usually exophytic and may encompass one or more teeth (Figure 4-35), spreading through penetration of the periodontal membrane. Occasionally, lesions arise from the periosteum overlying edentulous areas.

RADIOGRAPHIC FEATURES

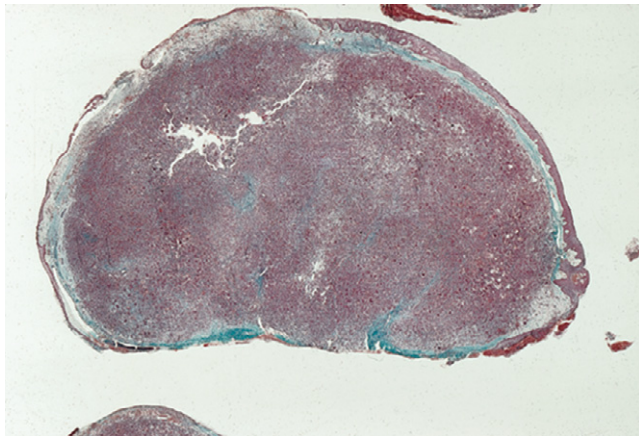
There may be little radiographic evidence of some lesions in teeth-bearing areas, because lesions may be small and primarily in the soft tissues. Larger lesions exhibit a superficial erosion of the cortical bone and may demonstrate some widening of the adjacent periodontal space. Close examination of the area may reveal small spicules of bone extending vertically into the base of the lesion (Figure 4-36, A). In edentulous areas, the cortical bone exhibits a concave area of resorption beneath the lesion, often referred to as *saucerization* (Figure 4-36, B). Radiographs are important to determine if the lesion is of gingival origin or of central origin with extension to the surface. If the lesion is of central origin, other predisposing conditions must be ruled out before a definitive diagnosis can be made.

HISTOPATHOLOGY

PGCG is composed of nodules of multinucleated giant cells in a background of mononuclear cells and extravasated red blood cells. Bands of fibrous connective tissue stroma containing small sinusoidal spaces (especially in the periphery) surround the nodules (Figure 4-37). Osteoid deposits or spicules of new bone are often present in the base of the lesion. Accumulations of hemosiderin are found throughout the lesion.



FIGURE 4-36
Peripheral giant cell granuloma. **A**, Periapical radiograph of mixed dentition area illustrating the lesion's extraosseous nature, lack of involvement of the underlying bone, erupting teeth, and presence of small bone spicules extending into the base of the lesion. **B**, Radiograph of bone beneath a lesion in an edentulous area of a patient who wears a denture, exhibiting the concave area of bone resorption ("saucerization").

**FIGURE 4-37**

Peripheral giant cell granuloma. Low-power photomicrograph of trichrome-stained tissue demonstrating the lack of mature collagen (blue-green) and the abundance of cells (red).

TREATMENT

Most lesions of PGCG respond well to thorough surgical curettage that exposes all bony walls. When the periodontal membrane is involved, the associated teeth may need to be extracted to accomplish complete removal. Occasionally, lesions may recur. This is not an indication for radical treatment.

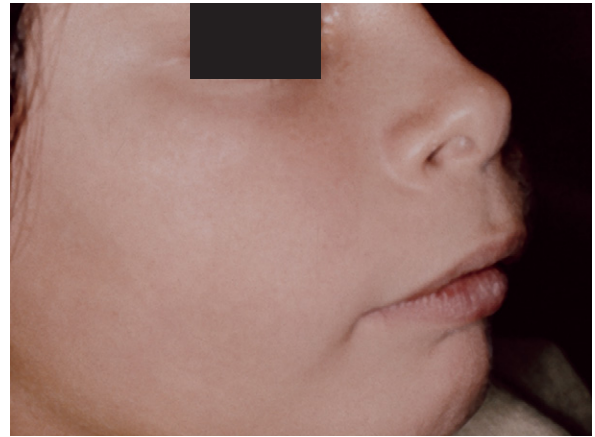
Central Giant Cell Lesion

CENTRAL GIANT CELL LESION: *An intraosseous destructive lesion of the anterior mandible and maxilla in which larger lesions expand the cortical plates, cause movement of teeth, and produce root resorption; it is composed of multinucleated giant cells in a background of mononuclear fibrohistiocytic cells and red blood cells.*

Central giant cell granuloma (CGCG) is a giant cell lesion that occurs centrally within the mandible and maxilla and is generally less aggressive and destructive compared with those occurring in the long bones. The more aggressive lesions commonly found in the long bones are rare in the jaws. However, lesions resembling the less destructive granulomatous jaw form of the disease can be occasionally found in the other skeletal bones.

CLINICAL FEATURES

CGCGs occur far less commonly than PGCG. The majority of lesions are found in patients in the 10- to 30-year-old age group. Lesions occur in the anterior mandible and maxilla (Figure 4-38), with nearly 75% located in the mandible and crossing the midline. Expansion of the buccal and lingual cortical plates is common. Some lesions exhibit cortical perforation and resorption of root apices. In other lesions a much less aggressive behavior is observed.

**FIGURE 4-38**

Central giant cell granuloma. Young patient with large lesion of anterior maxilla producing a midface deformity.

RADIOGRAPHIC FEATURES

The radiographic appearance of CGCG is not specific for this condition. It consists of a radiolucency (usually relatively large) with an indistinct line of demarcation with the adjacent normal bone. Buccal and lingual expansion is usually observed on occlusal radiographs, which often exhibit complete cortical bone loss. Movement of associated teeth and resorption of tooth roots is commonly observed (Figure 4-39).

HISTOPATHOLOGY

Tissue from the lesions is composed of giant cells, usually containing 5 to 20 nuclei, against a background of mononuclear cells and fibrous tissue (Figure 4-40). In less aggressive lesions, the giant cells are within distinct nodules separated by wide zones of cellular fibrous tissue. In the more granulomatous lesions, foci of new bone formation are evidenced by osteoid and woven bone. In the more aggressive lesions, the proportion of mononuclear cells and giant cell tissue is greatly increased, mature fibrous tissue is decreased, and foci of bone formation are lacking. Although grading the degree of aggressiveness is possible to a certain extent based on an assessment of the features of the lesion, it is difficult in most cases.

TREATMENT

Most cases of CGCG are successfully treated by curettage. Occasionally, lesions will recur and require one or more retreatments. Recent reviews of reports containing large numbers of patients indicate that the younger the patient, the greater the tendency of recurrence. Block resection is sometimes required because of the size, initial presentation, or anatomic location of the lesion. Radiotherapy is contraindicated.



FIGURE 4-39

Central giant cell granuloma. Panoramic radiographs of patient in Figure 4-38 revealing large area of ill-defined radiolucency of anterior maxilla, displacement of teeth, and resorption of root apices (**A**) and more common location of the anterior mandible in which the patient exhibits a lesion extending from the left cuspid to the right first molar (**B**).

Aneurysmal Bone Cyst

ANEURYSMAL BONE CYST: An uncommon lesion located primarily in the posterior mandible and maxilla with clinical features similar to central giant cell lesion; it contains many large blood-filled spaces separated by connective tissue septa containing giant cell tissue.

Aneurysmal bone cyst (ABC) is uncommon and is considered a variant of CGCG. It differs primarily by containing many large blood-filled spaces separated by bands of fibrous tissue containing giant cells. Blood flows through the spaces at pressure levels too low to produce the bruit sounds that can sometimes be heard in the similar-

appearing intraosseous hemangioma. ABC is commonly found in association with other intraosseous lesions, giving credence to the popular hypothesis that ABC is a secondary phenomenon to other events occurring in bone. The most commonly associated conditions are benign and malignant bone tumors, fibrous dysplasia, traumatic bone cyst, and intraosseous hemangioma.

CLINICAL FEATURES

In the jaws, ABC occurs in the first three decades of life, with a peak incidence in patients in the 10- to 19-year-old age group. Most lesions occur in the posterior mandible and often extend into the ramus. The occasional lesion that occurs in the maxilla is also confined

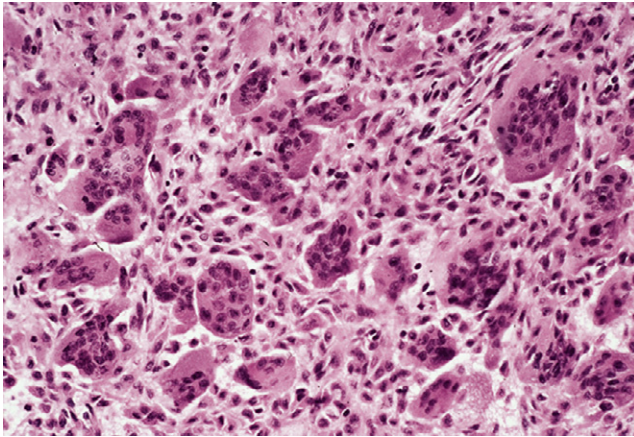


FIGURE 4-40
Central giant cell granuloma. Microscopic features include large multinucleated cells in a fibrohistiocytic background.

to the molar area (Figure 4-41). Lesions are firm, diffuse swellings that produce facial deformity and malocclusion. ABC grows rapidly and may perforate the cortex.

RADIOGRAPHIC FEATURES

The radiographic features are not distinctive, consisting of an oval or fusiform expansile radiolucency in which the cortex is thinned or eroded. Teeth are often moved and their roots resorbed. Lesions are usually unilocular, with some exhibiting faint trabeculation.

HISTOPATHOLOGY

ABC tissue consists of large blood-filled spaces separated by fibrous septa. The septa are composed of connective tissue containing osteoid deposits, spicules of woven bone, and deposits of hemosiderin (Figure 4-42). Varying numbers of multinucleated giant cells may be observed.

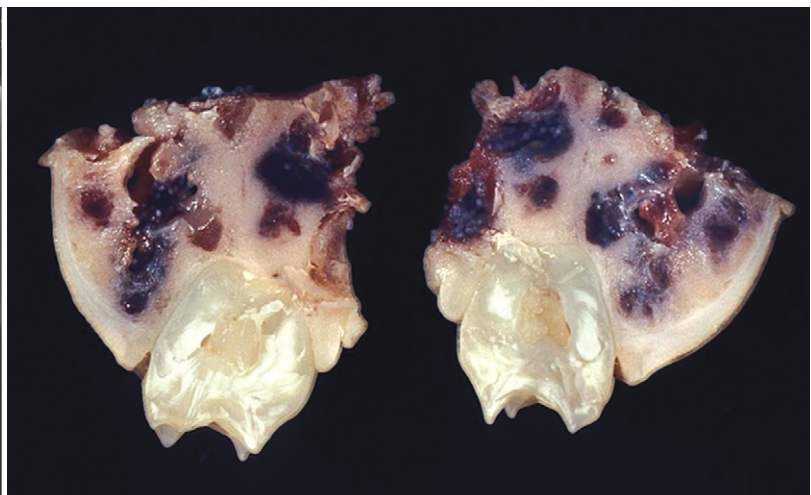


FIGURE 4-41
Aneurysmal bone cyst. **A**, Computed tomography of large lesion of posterior right maxilla exhibits extension into the sinus and right nasal passage. **B**, Cross section through a gross specimen revealing the multiple large blood-filled spaces, loss of the normal trabecular bone, expansion of the cortices, and resorption of the molar tooth roots.

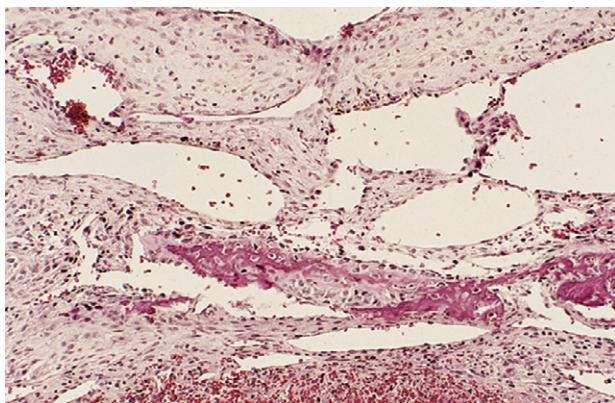


FIGURE 4-42
Aneurysmal bone cyst. Microscopic appearance reveals multiple sinusoidal spaces without an endothelial cell lining, separated by cellular fibrous septa, containing fibrohistiocytic cells and islands of bone formation. Some lesions also will contain foci of multinucleated giant cells.

TREATMENT

ABC is usually treated by curettage. Lesions recur in 20% of cases and are retreated in the same manner. Treatment is often coordinated with that of the associated lesion.

TRAUMATIC BONE CYST

TRAUMATIC BONE CYST: *Asymptomatic intraosseous empty cavity of young patients located primarily within the mandible and lined by a thin loose connective tissue membrane; it is adequately treated when blood enters the space during an intraosseous biopsy.*

The traumatic bone cyst, also termed *simple bone cyst*, *hemorrhagic bone cyst*, and *idiopathic bone cavity*, is an intrabony cavity that spontaneously occurs in the mandible of young patients. Although the cause of this lesion is unclear, it is commonly thought to occur after a traumatic injury in which faulty resolution or lysis of the intramedullary hemorrhage results in the formation of an empty bone cavity.

CLINICAL FEATURES

The predominant site of occurrence is the molar and premolar region of the mandible. Most lesions occur in patients under 20 years of age. A slight female predilection has been reported. Lesions are asymptomatic and are generally discovered during routine radiographic examination. Surgical exploration of the lesion reveals a cavity that may be empty or contain a small amount of serous or serosanguineous fluid.



FIGURE 4-43

Traumatic bone cyst. Radiograph of mandible demonstrating a large well-circumscribed radiolucency extending superiorly between the roots of the teeth, producing a characteristic scalloped appearance.

RADIOGRAPHIC FEATURES

Traumatic bone cyst appears as a well-circumscribed, solitary radiolucency of variable size. Larger lesions frequently extend between the roots of the associated teeth to produce a scalloped appearance that is characteristic of this lesion (Figure 4-43). Although buccal or lingual cortical expansion of the mandible is usually absent, it has been reported in some cases.

HISTOPATHOLOGY

Tissue obtained from the wall of the lesion reveals a thin layer of loose and delicate connective tissue overlying a zone of reactive bone that exhibits remodeling. Often the soft tissue luminal surface contains a thin layer of fibrin (Figure 4-44, A). In areas where healing is taking place, the connective tissue will contain mineralized deposits of new bone with a distinctive lamellar pattern (Figure 4-44, B).

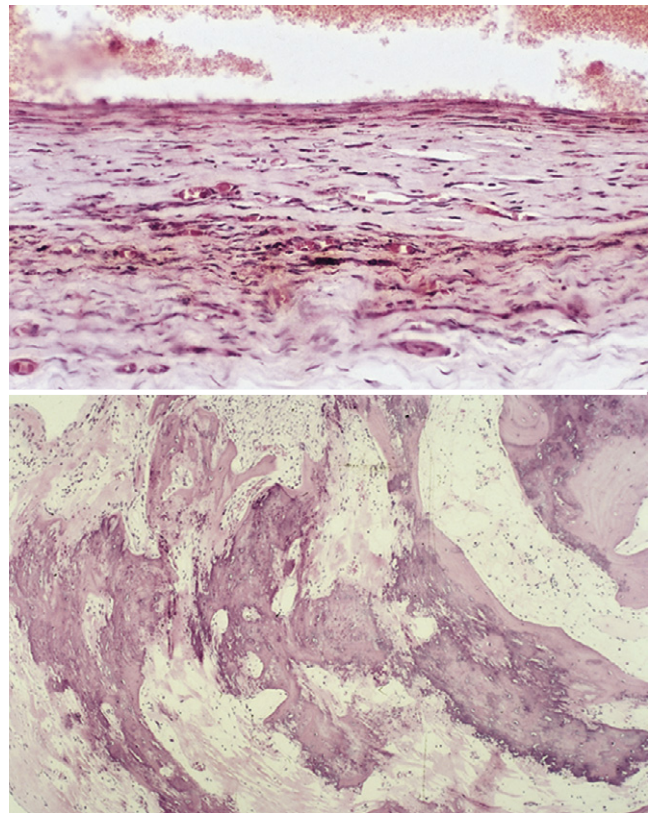


FIGURE 4-44

Traumatic bone cyst. **A**, Photomicrograph of active lesion reveals a thinned connective tissue lining surrounding a lumen that contains a thin layer of fibrin on the luminal surface and deposits of hemosiderin. **B**, In areas in which healing has begun, the tissues display a distinctive lamellar pattern of mineralization and new bone formation within the regenerating connective tissue.

TREATMENT

Surgical hemorrhage induced during diagnostic exploration and curettage of the cavity is usually all that is required to achieve complete resolution of the lesion. A thin membrane compartmentalizes some lesions, requiring penetration of the individual spaces and curettage of the walls to induce hemorrhage in all cavities. Caution is required in large lesions to prevent severance of the neurovascular bundles extending from the inferior alveolar nerve to the area's vital teeth. The frequency of this lesion in patients younger than 25 years and its rarity after that time suggest that most lesions resolve spontaneously, because not all lesions are found and treated. Surgical exploration is still advised to rule out more serious disease and to facilitate healing.

LANGERHANS CELL HISTIOCYTOSIS

LANGERHANS CELL HISTIOCYTOSIS: *A probable neoplastic proliferation of Langerhans type of histiocytic cells with a wide spectrum of biologic behavior ranging from a single lesion of the mandible to diffusely distributed bone lesions in combination with organ and other soft tissue lesions; consists of S-100 and CD1a positive histiocytes containing Birbeck granules and accompanying accumulations of eosinophils.*

The principal cells of the histiocytic system are the mononuclear phagocyte, the dendritic Langerhans cell, and the lymph node follicular dendritic cell. The cell type most commonly involved in a proliferative disorder is the Langerhans cell, and the disease is designated as Langerhans cell histiocytosis (LCH). It is estimated that LCH occurs at the rate of 0.2 to 0.5 cases per 100,000 children

per year. Controversy regarding the cause and pathogenesis of LCH is reflected in the many and varied names applied to it. Lesions with the same basic histopathologic features were originally considered three separate diseases: (1) Letterer-Siwe disease, (2) Hand-Schüller-Christian disease, and (3) eosinophilic granuloma. The hypothesis that all three conditions were essentially one disease process with multiple clinical manifestations led to a variety of names, the most prevalent being *histiocytosis X*, because it acknowledged both the proliferation of histiocytes and the unknown causative factor (X).

More recently, terms such as *idiopathic histiocytosis*, *Langerhans cell granuloma*, and *Langerhans cell disease* have been used to indicate that the cause is unknown but the process is most likely a condition of immune cells. The current name—*Langerhans cell histiocytosis*—reflects the consensus regarding the basic cause as published in 1987 by the Histiocyte Society. The studies leading to these conclusions used DNA technology on cells from each of the clinical disease types and determined that the cells were a single clonal proliferation of the CD1a-positive Langerhans cell. The single clonality of the cell type is strong evidence that the disease process is neoplastic rather than a polyclonal immunoreactive process.

CLINICAL FEATURES

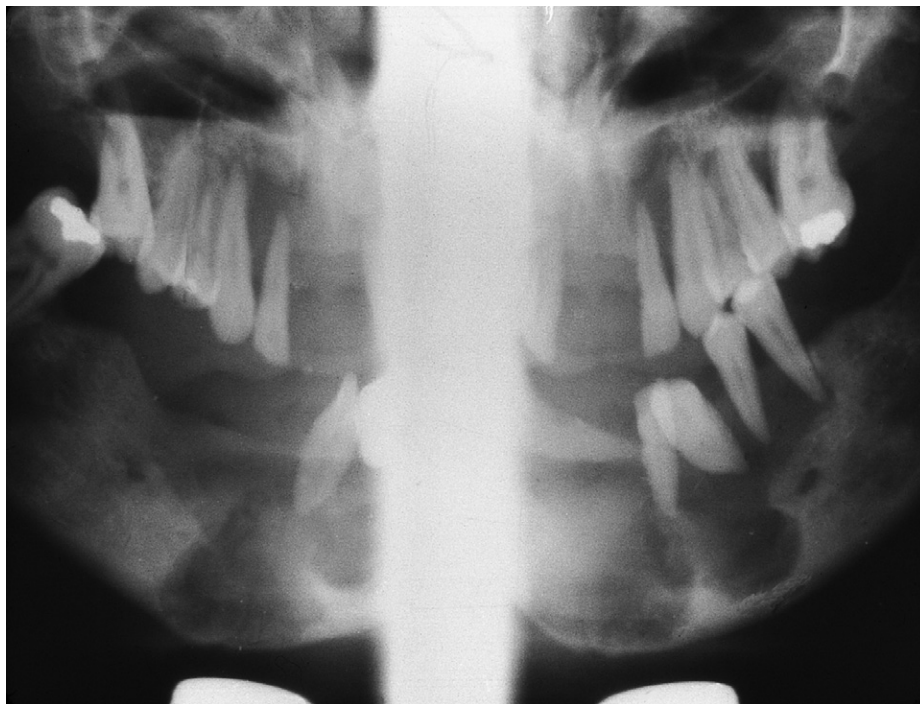
LCH has a wide clinical spectrum of prognosis and severity of involvement. Depending on the patient's age of onset and distribution of the lesions, it has been clustered into three clinical syndromes, all of which may have the same histopathologic tissue findings. Assessing the degree of cellularity and atypia of the lesional tissue has not shown a reliable indication of prognosis. More accurate information is obtained by a determination of



FIGURE 4-45
Langerhans cell histiocytosis. Periapical radiograph of intraosseous lesion of chronic focal form (“eosinophilic granuloma”) located in crestal bone between molars.



FIGURE 4-46
Langerhans cell histiocytosis. Lesion affecting the crestal bone in localized area presenting clinically as an area of advanced periodontal disease.

**FIGURE 4-47**

Langerhans cell histiocytosis. Panoramic radiograph of mandibular involvement in patient with chronic disseminated disease in which the teeth appear to be floating in space.

the number of affected bones and organs and other bodily dysfunctions.

Based on the clinical findings, LCH is grouped into three categories for treatment and prognostic purposes: (1) *chronic focal*—usually a solitary lesion in one bone but occasionally in multiple bones, with no soft tissue or organ involvement (previously designated as “eosinophilic granuloma”); (2) *chronic disseminated*—involving multiple bones, organs, lymph nodes, and occasionally skin (previously designated as “Hand-Schüller-Christian disease”); and (3) *acute disseminated*—involving most organs, lymph nodes, bone marrow, and skin of infants (previously designated as “Letterer-Siwe disease”).

RADIOGRAPHIC FEATURES

In the oral cavity the chronic focal form of LCH (“eosinophilic granuloma”) occurs with the greatest frequency. It commonly appears in teenagers and young adults as an area of discomfort in which radiographs reveal a solitary intraosseous punch out lesion around and beneath the teeth roots (Figure 4-45). The lesions may involve several teeth (Figure 4-46) and appear as focal areas of advanced periodontal disease in which the teeth seem to be floating in space because of the lack of surrounding bone (Figure 4-47). In edentulous or nontooth-bearing areas, the lesion presents as a demarcated radiolucency (Figure 4-48). In other areas the lesion closely resembles

**FIGURE 4-48**

Langerhans cell histiocytosis. Occlusal radiograph of large lesion of focal chronic form of the disease in anterior mandible of edentulous patient.

a large periapical abscess with teeth erroneously treated endodontically. The discovery of one lesion should be followed by a survey of the rest of the jaws, skull, ribs, vertebrae, and skeletal bones to determine if multiple bones are involved. The chronic disseminated form (“Hand-Schüller-Christian disease”) has bone lesions similar to the chronic focal form and also soft tissue lesions. This

form tends to occur most commonly in patients under 10 years of age. The status of the acute disseminated form ("Letterer-Siwe disease") is in question, because many believe that cases attributed to this form may represent other disease processes such as acute forms of lymphoma. Patients are usually infants who follow a rapidly fatal course because of extensive involvement of skin and visceral organs by anaplastic cells.

HISTOPATHOLOGY

Except for the acute disseminated form of the disease, the microscopic features of the tissue have a remarkable similarity. The tissue contains sheets of large histiocytic cells with eosinophilic cytoplasm and centrally placed nuclei with occasional multinucleated cells interspersed with other inflammatory cells (Figure 4-49, A). Of par-

ticular note is the presence of abundant focal concentrations of eosinophils (Figure 4-49, B), a histopathologic feature useful in differentiating common periapical and periodontal inflammatory lesions of the jaws from LCH.

The presence of Birbeck granules when viewed with electron microscopy confirms a diagnosis of LCH. These intracytoplasmic structures are unique in mononuclear Langerhans histiocytic cells and appear either as elongated thin rods or tennis racket-shaped (Figure 4-50). Using immunohistochemistry, the mononuclear histiocytic cells are S-100 and CD1a-positive (Figure 4-51).

TREATMENT

For the focal chronic forms ("eosinophilic granuloma") that are easily accessible to surgical intervention, thorough curettage is the treatment of choice. For more diffusely

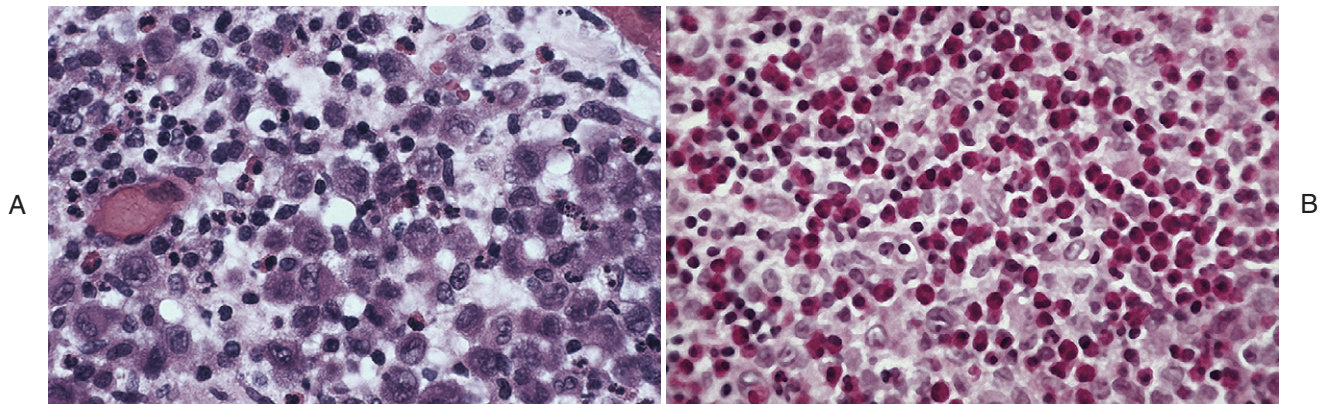


FIGURE 4-49

Langerhans cell histiocytosis. Photomicrographs of large sheets of Langerhans histiocytic cells (A) and histiocytic and eosinophilic cells (B).

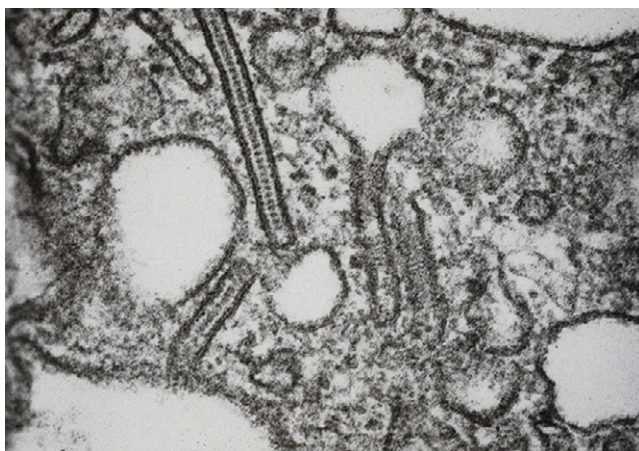


FIGURE 4-50

Langerhans cell histiocytosis. Ultrastructure of Langerhans histiocytes reveals rods and tennis racket-shaped intracytoplasmic structures.

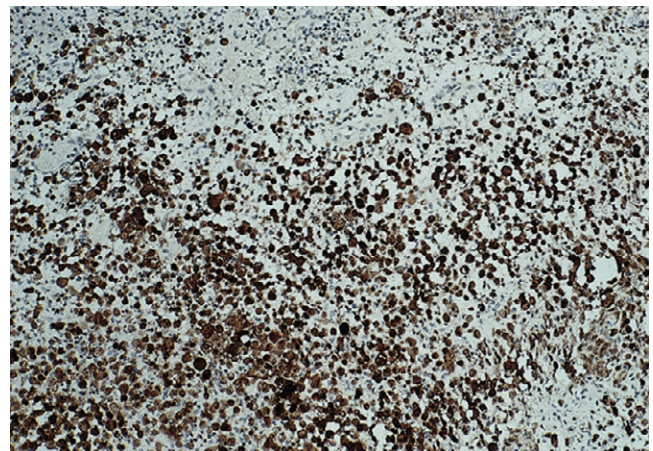


FIGURE 4-51

Langerhans cell histiocytosis. Photomicrograph of positive staining (brown) of histiocytes with S-100 immunostain.

located inaccessible lesions, chemotherapy with cytotoxic agents is commonly used. Recurrence and the development of new lesions are often problematic, requiring long-term follow-up.

MALIGNANT TUMORS

OSTEOGENIC SARCOMA

OSTEOGENIC SARCOMA: *Most common of the malignant neoplasms derived from bone cells that in the jaws exhibit radiographic widening of periodontal membrane of teeth and histologically exhibit a wide spectrum of findings, all of which contain atypical osteoblasts and abnormal bone or osteoid formation.*

Osteogenic sarcoma is the most common malignant tumor of bone cells, occurring in 1 of every 100,000 people. It most commonly occurs in the long bones, having a predilection for the distal and proximal areas of the femur, tibia, and humerus. Approximately 7% of osteogenic sarcomas occur in the head and neck area. Many conditions predispose individuals to osteogenic sarcoma. Because a substantial increase in incidence of osteogenic sarcoma occurs in patients with retinoblas-

toma, it is now thought that the RB1 gene (13q14.1-q14.2) causes both retinoblastoma and osteogenic sarcoma. Lesions also commonly develop in bones beneath soft tissue that has received prior radiation treatments. The incidence of osteogenic sarcoma in older patients with a history of Paget disease of bone is 1%, a substantial increase over the incidence in the normal population. In those patients, findings suggest that the association between Paget disease and osteogenic sarcoma is the result of a single gene or two tightly linked genes on chromosome 18.

CLINICAL FEATURES

The peak incidence of osteogenic sarcoma of the jaws is 10 years later than the peak in the long bones, having a mean onset age of 33 years rather than 24 years of age. Lesions of the mandible and maxilla are usually first noticed as bony, hard swellings of the buccal and lingual cortices (with or without pain) and often associated with separation of teeth (Figure 4-52). In some patients, lesions occur as exophytic hard nodules on the attached gingiva, appearing as soft tissue epulides (Figure 4-53). Such lesions are uncommon and have been termed *juxtacortical osteogenic sarcomas*. These lesions were previously separated into parosteal and periosteal variants. This distinction is now considered unnecessary, because the lesions seem to be variations of the same entity. Both arise in tissues external to the bone (either in or near the periosteum), rather than from the usual endosteal origin.

RADIOGRAPHIC FEATURES

The radiographic appearance of osteogenic sarcoma varies considerably, depending on the specific histopathologic type. Some lesions, such as the telangiectatic or fibrohistiocytic types, have little bone formation and



FIGURE 4-52
Osteogenic sarcoma. Lesion of anterior mandible exhibiting buccal (A) and lingual swelling and separation of teeth (B).



FIGURE 4-53
Juxtacortical osteogenic sarcoma. Exophytic lesion of anterior maxilla.



FIGURE 4-54
Osteogenic sarcoma. Periapical radiograph of lesions in Figure 4-52 (A) and Figure 4-53 (B) exhibiting mottling of alveolar bone and characteristic widening of the periodontal membrane.

are radiolucent. Lesions of the well-differentiated osteoblastic and chondroblastic types of osteogenic sarcoma form large amounts of mineralized bonelike tissue, producing large areas of radiopacity within a diffuse, non-defined radiolucent background. A characteristic finding in jaw lesions is widening of the periodontal membrane in adjacent teeth (Figure 4-54). Although this finding is not unique to osteogenic sarcoma, it is sufficiently consistent to be of diagnostic value. An occlusal radiograph usually reveals a sunburst pattern of radiopacity radiating from the periosteum (Figure 4-55). This pattern is also not exclusive to osteogenic sarcoma but assists in the diagnosis.

HISTOPATHOLOGY

Four intraosseous variants and one juxtacortical histologic variant of osteogenic sarcoma have been described. Osteogenic sarcoma lesions must contain normal or abnormal osteoid or bone that is closely associated with the malignant connective tissue cells to distinguish them from other forms of sarcoma (Figure 4-56).

Intraosseous variants are separated according to the variability in the sarcomatous component and the amount and nature of the hard tissue component (Box 4-3). The osteoblastic type is the most common (particularly in the extremities) and contains a relatively equal distribution of the pleomorphic and hyperchromatic sarcomatous cell component and the hypercellular trabecular bone. The chondroblastic type contains deposits of hypercellular cartilage and abnormal os-

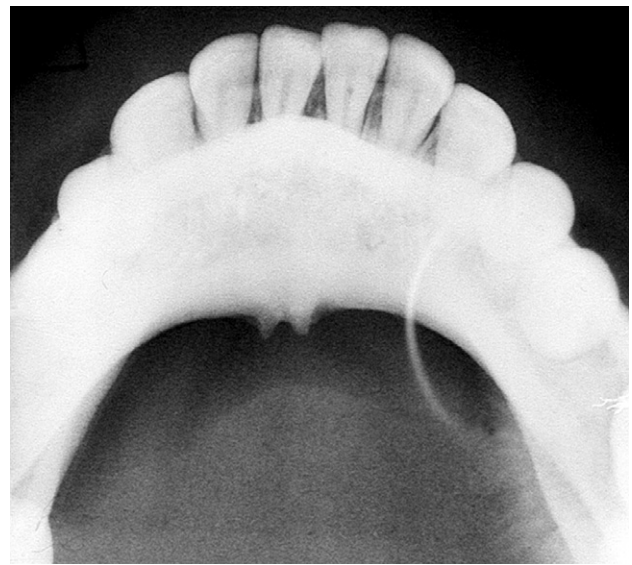
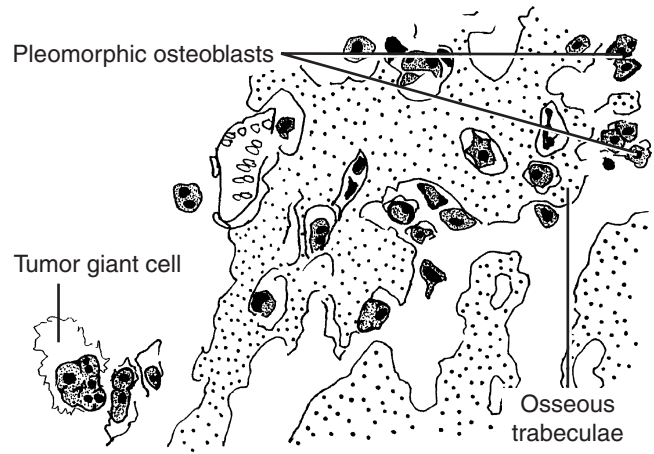
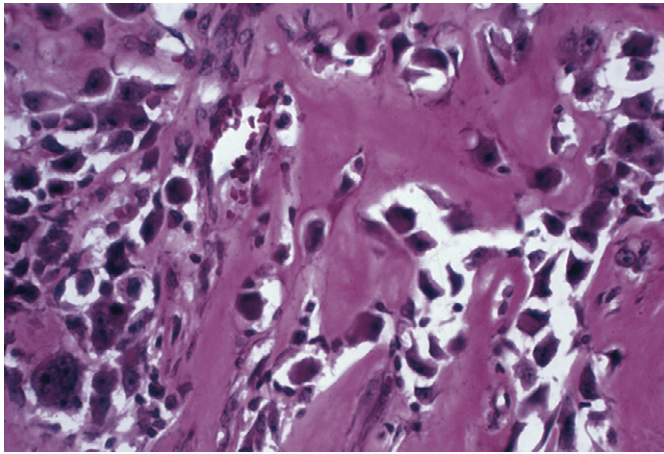


FIGURE 4-55
Osteogenic sarcoma. Occlusal radiograph of lesion in posterior right mandible with commonly observed sunburst pattern of radiopacity.

teoid and bone. This variant is common in the jaws. Fibroblastic osteogenic sarcoma is composed of sarcomatous spindle-shaped cells with little malignant osteoid. On radiographs these lesions may appear completely radiolucent. Telangiectatic lesions have a

**FIGURE 4-56**

Osteogenic sarcoma. Photomicrograph of malignant cells surrounding and within abnormal bone.

BOX 4-3

Histologic Variants of Intraosseous Osteosarcoma

Osteoblastic
Chondroblastic
Fibroblastic
Telangiectatic

reduced hard tissue component and a greatly increased number of enlarged blood vessels and giant cells.

Juxtacortical (parosteal) lesions are located above the periosteum and are low-grade osteoblastic lesions containing large separate areas of malignant cartilage. Lesions are usually nodular and may only contact the cortical bone in focal areas.

TREATMENT

Treatment is usually a combination of surgical resection that produces a wide margin of normal bone followed by extensive chemotherapy. The prognosis seems to be better in the mandible than in the rest of the skeleton. Patients with juxtacortical osteogenic sarcoma fare better in both skeletal and jaw locations.

CHONDROSARCOMA

CHONDROSARCOMA: Uncommon malignant bone neoplasm in the jaws, usually of the anterior maxilla, consisting of a proliferation of plump chondroblasts or spindle-shaped mesenchymal cells and abnormal cartilage but no osteoid or bone.

Chondrosarcomas are malignant bone tumors in which the malignant cells produce abnormal cartilage exclusively and no osteoid or bone. Lesions may be *primary chondrosarcomas* (arising directly from bone cells as malignant neoplasms) or *secondary chondrosarcomas* (arising in a preexisting benign cartilaginous lesion such as enchondroma or osteochondroma). Lesions have been associated with Paget disease, Ollier disease (multiple enchondromatosis), and Maffucci syndrome (multiple enchondromatosis, hemangiomas, and fibromas). In the jaws, nearly all chondrosarcomas arise de novo without the preexistence of benign chondromas.

CLINICAL FEATURES

Chondrosarcoma of the jaws occurs at any age but has a peak incidence in patients in the 30- to 40-year-old age group. Nearly all lesions are confined to the anterior maxilla, where preexisting nasal cartilage is present, and the premolar areas of the mandible, the site of the embryonically derived Meckel cartilage.

Lesions are expansile masses that produce distortion of the areas (Figure 4-57). In the larger lesions, pain and paresthesia may occur. In the anterior maxilla, nasal obstruction and breathing difficulties are often presenting signs.

RADIOGRAPHIC FEATURES

The radiographic appearance can be variable depending on the extent of calcification of the cartilaginous component. Commonly, it appears as an expansile “moth-eaten” radiolucent area with indistinct boundaries containing flecks or blotchy radiopacities throughout (Figure 4-58). Widening of the periodontal membrane of associated teeth is a common finding.



FIGURE 4-57
Chondrosarcoma. Lesion of anterior right mandible with minor movement of teeth.

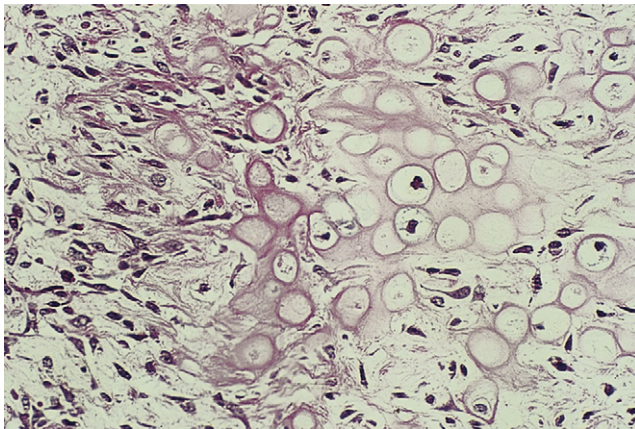


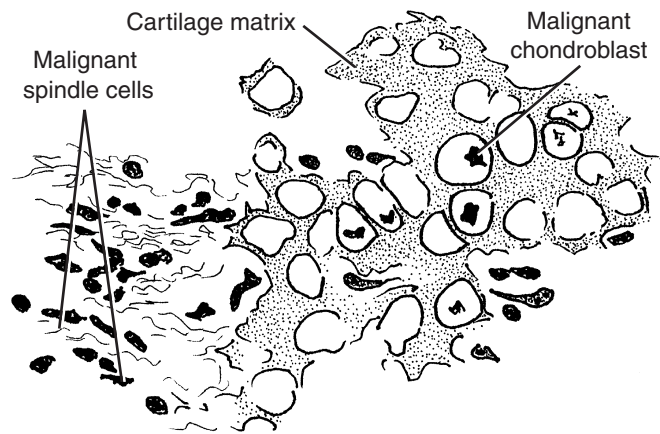
FIGURE 4-59
Chondrosarcoma. Photomicrograph exhibiting malignant cells both within and surrounding deposits of abnormal cartilage.

HISTOPATHOLOGY

A great deal of variability may occur in the histologic features of chondrosarcoma, because they may be well-differentiated and resemble a benign cartilaginous lesion or they may be anaplastic, composed of spindled cells with little evidence of cartilage formation. Most lesions exhibit a combination of abnormal cartilage surrounded by neoplastic cells (Figure 4-59). Lesions are graded I to III, depending on the amount and maturity of the cartilage and the proportion and anaplasticity of the connective tissue cells. In grades II and III, areas of myxoid tissue and cystic degeneration are present.



FIGURE 4-58
Chondrosarcoma. Computed tomography of large lesion of left maxilla containing flecks of radiopacities.

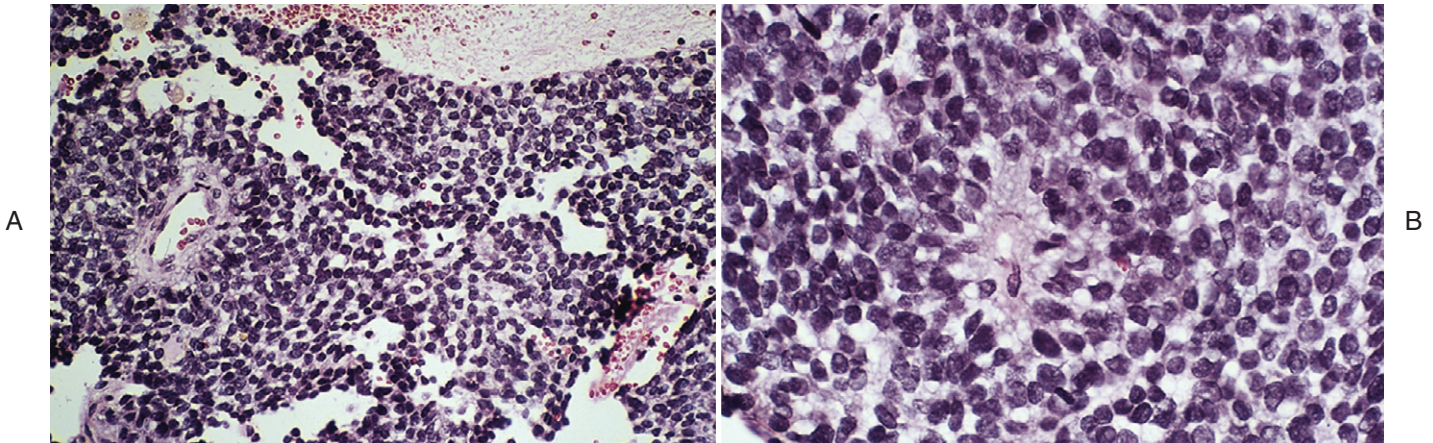


TREATMENT

Treatment consists of wide surgical excision. The extent of the surgical margin depends on the size and grade of the lesion. Metastasis is usually to the lungs and other bones. The prognosis for jaw lesions is worse than for lesions occurring in other locations.

EWING SARCOMA

EWING SARCOMA: Rare malignant bone neoplasm of uncertain cell origin in young patients; the lesion is composed of anaplastic small, dark, round cells containing glycogen granules and intermediate filaments.

**FIGURE 4-60**

Ewing sarcoma. **A**, Low-power photomicrograph reveals sheets of small, dark, rounded cells with scant amounts of stromal tissue. **B**, High-power photomicrograph displays malignant cells with rounded nuclei and ill-defined cytoplasm in characteristic cluster arrangement around vascular structure.

Ewing sarcoma is a highly malignant bone tumor thought to arise from primitive neuroectodermal cells. The lesions consist of densely packed, small, darkly stained round cells without prominent nucleoli or distinct cell borders. Although the histogenesis is still not completely resolved, Ewing sarcomas and related peripheral primitive neuroectodermal tumors have enough genetic features in common to be referred to as *Ewing sarcoma of family tumors (ESFT)*. The genetic hallmark of ESFT is the presence of the t(11; 22)(q24; q12) translocation, which creates the EWS/FLI1 fusion gene and results in the expression of a chimeric protein. Major studies have observed that the early region (E1A) of human adenovirus type 5 is directly linked to and may initiate production of the EWS/FLI1 fusion transcript in normal human fibroblasts and keratinocytes. Ewing sarcoma comprises 10% of the malignant bone tumors. It is rarely seen in Chinese, African, and African-American patients. It has been found in family clusters and in patients with birth defects and is most common in the femur and pelvic bones, with only 1% of lesions affecting the jaws. The exact incidence is difficult to determine, because lesions closely resemble non-Hodgkin lymphoma and neuroblastoma.

CLINICAL FEATURES

Ewing sarcoma has a predilection for younger patients, usually children and adolescents; it is rarely seen in patients more than 30 years old. Patients usually have slight to moderate fever, leukocytosis, and increased sedimentation rates. In the area of involve-

ment, pain is concurrent with rapid swelling. In the jaws, patients may experience loosening teeth and, in later stages, focal ulceration. It is present in the craniofacial bones in approximately 4% of cases. The mandible is affected more often than the maxilla, cranial base, and skull.

RADIOGRAPHIC FEATURES

The involved bone appears “moth-eaten,” simulating an osteomyelitis with indistinct margins. The periosteum often has a lamellar layering, referred to as an “onion-skin” reaction.

HISTOPATHOLOGY

The histologic features are sufficiently nonspecific such that routine light microscopic evaluation is insufficient for diagnosis. It usually requires additional stains, electron microscopy, or immunohistochemical markers. Individual cells may be of two types: (1) small and round, with darkly staining nuclei and a visibly delineated cytoplasm, and (2) larger, with a finely granular nucleus and a faint ill-defined cytoplasm. Both cell types are undifferentiated cells (Figure 4-60), similar to those present in many other primary or metastatic undifferentiated neoplasms that occur in bone.

Silver nitrate staining reveals septa surrounding lobules of cells. Both PAS stains and ultrastructural studies demonstrate characteristic glycogen granules in neoplastic cells. Immunomarkers are used to rule out other tissues of origin and establish the presence of vimentin-positive intermediate filaments.

TREATMENT

The anaplastic nature of the neoplastic cells makes the neoplasm sensitive to both chemotherapy and radiotherapy. Surgery is sometimes used for small lesions in conjunction with the other modalities. Lesions metastasize early to lungs and other bones. Prognosis depends on the extent of metastasis and the effectiveness of chemotherapy. In general, a 30% local recurrence rate is seen within 5 years. Lesions of the mandible have the most favorable survival rate of any site in the body.

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5 Odontogenic Tumors

CHAPTER OUTLINE

REVIEW OF ODONTOGENESIS

EPITHELIAL ODONTOGENIC TUMORS

Ameloblastoma
 Common Ameloblastoma
 Unicystic Ameloblastoma
 Peripheral Ameloblastoma
 Calcifying Epithelial Odontogenic Tumor
 Adenomatoid Odontogenic Tumor
 Calcifying Odontogenic Cyst
 Squamous Odontogenic Tumor

CONNECTIVE TISSUE ODONTOGENIC TUMORS

Odontogenic Fibroma
 Peripheral Odontogenic Fibroma
 Central Odontogenic Fibroma
 Odontogenic Myxoma
 Cementoblastoma

MIXED ODONTOGENIC TUMORS

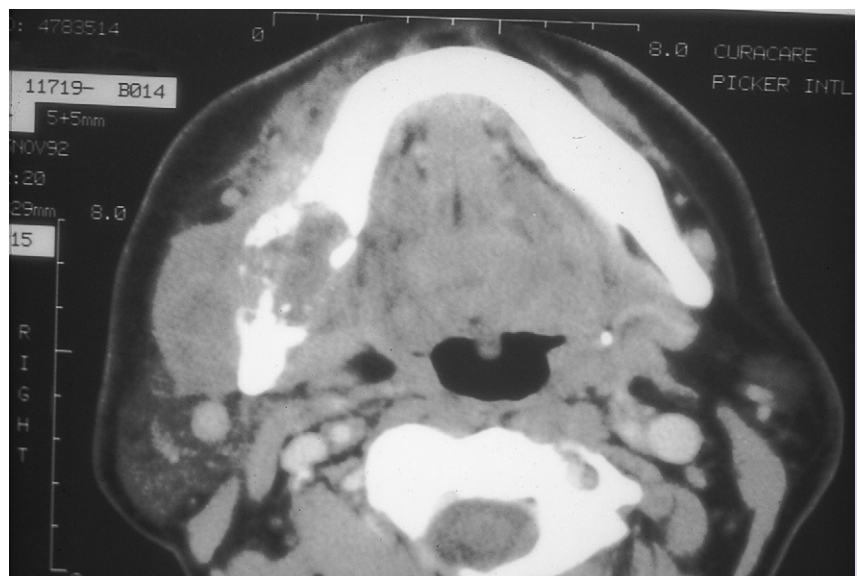
Ameloblastic Fibroma
 Odontoma
 Ameloblastic Fibro-Odontoma

MALIGNANT ODONTOGENIC TUMORS

Malignant Ameloblastoma
 Ameloblastic Carcinoma
 Odontogenic Carcinoma
 Primary Intraosseous Carcinoma

ADDITIONAL KEY TERMS

Complex odontoma
 Compound odontoma
 Desmoplastic ameloblastoma
 Intraluminal unicystic ameloblastoma
 Mural unicystic ameloblastoma
 Odontoameloblastoma
 Plexiform unicystic ameloblastoma



Odontogenic tumors are unique to the jaws and originate from tissue associated with tooth development. The abnormal tissue in each of these tumors can often be correlated with similar tissue in normal odontogenesis from inception to tooth eruption. The following brief review of odontogenesis will aid the understanding of these tumors.

REVIEW OF ODONTOGENESIS

Tooth formation originates during embryogenesis, arising from the oral epithelium covering the maxillary and mandibular alveolar processes. It begins as a budding of the basal cell layer over each specific location where teeth will occur. The epithelial bud elongates in the form of a solid tubelike structure that penetrates the connective tissue, a process known as *invagination* (Figure 5-1, A). The elongated epithelial structure is referred to as the *dental lamina* and is the dentition's source of all future activity and differentiation relative to development. When the appropriate depth is reached, the basal cell layer at the tip of the dental lamina thickens, forming a concavity. This structure represents the cap stage of tooth development (Figure 5-1, B). As odontogenesis proceeds, the cap-shaped structure enlarges and the bottom layer of epithelium (inner enamel epithelium) separates from the top layer (outer enamel epithelium). The intervening zone is composed of loosely arranged star-shaped epithelial cells (stellate reticulum). A concurrent elongation of the periphery of the epithelial structure takes place, shaping the future crown of the tooth specific for that location.

This stage is referred to as the *early bell stage* (Figure 5-1, C). This specialized epithelium induces the

adjacent connective tissue to be modified into a circumscribed zone of embryonic and myxomatous connective tissue that may be further induced to form dentin or pulp tissue. The altered connective tissue around which the future tooth root will form is termed the *dental papilla*. Induction of the connective tissue surrounding the entire embryonic tooth structure also occurs at this stage of odontogenesis. This outer zone of connective tissue that encapsulates the developing tooth bud is dense and fibrous and is referred to as the *dental follicle*. The dental follicle remains around the tooth until it erupts; the crown portion of the follicle becomes part of the connective tissue of the free marginal gingiva, and the root portion becomes the periodontal ligament that separates the bone from the cementum.

During the late bell stage (Figure 5-1, D) the cells of the inner enamel epithelium become elongated and palisaded. Concurrent migration of the nucleus away from the basement membrane occurs, a process referred to as *reverse polarization*. This event indicates the cells' change to presecretory ameloblasts. Reverse polarization induces the undifferentiated cells in the adjacent dental papilla to differentiate into presecretory odontoblasts that align in a palisaded manner against the basement membrane opposite the presecretory ameloblasts. As the ameloblasts mature, the odontoblasts are stimulated to secrete dentin matrix that in turn initiates the deposition of enamel matrix on the opposite side of the basement membrane. During this stage of odontogenesis, the dental lamina begins to break up and forms small islands in the connective tissue. These islands of residual epithelium are inactive and referred to as *rests of the dental lamina* or *rests of Serres*.

After the specific shape of a tooth crown has been completed (Figure 5-2, A), the epithelium that forms

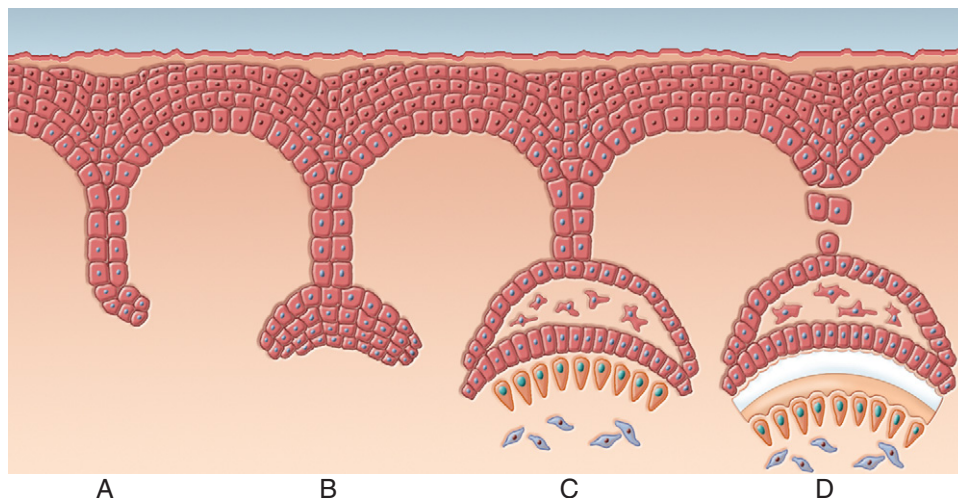
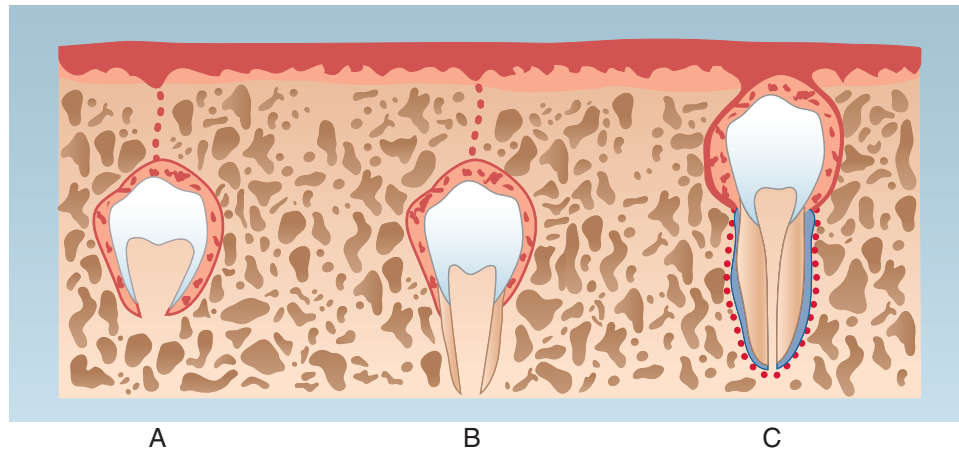


FIGURE 5-1
Early stages of odontogenesis. A, Invagination. B, Cap stage. C, Early bell stage. D, Late bell stage.

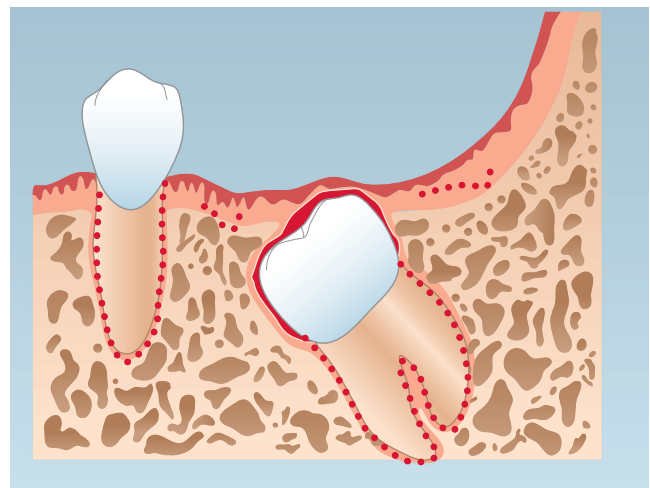
**FIGURE 5-2**

Later stages of odontogenesis. **A**, Crown formation and remnants of dental lamina.

B, Root formation. **C**, Preeruption completed tooth formation and rests of Malassez (red dots).

the outer rim of the bell-shaped enamel organ elongates, forming the shape and length of the roots (Figure 5-2, *B*). This epithelium forms a thin transient membrane referred to as *Hertwig root sheath*. In this location, odontoblasts form to produce the dentin necessary for root formation. When the root is nearly complete, the continuity of the epithelial root sheath begins to break down, first becoming porous and eventually becoming completely fragmented. This allows the connective tissue cells from the dental follicle adjacent to the root to encounter the newly formed dentin. The dentin stimulates these cells to differentiate into cementoblasts. Cementoblasts are responsible for generating the calcified layer over the dentin, referred to as *cementum*.

Cementum serves to anchor the collagen fibers of the dental follicle and periodontal ligament to the tooth root and to seal the outer side of the dentinal tubule. The epithelial remnants of Hertwig root sheath remain in the periodontal ligament after tooth formation is complete and are referred to as *rests of Malassez* (Figure 5-2, *C*).

**FIGURE 5-3**

Possible epithelial sources of ameloblastoma (represented by red color): Remnants of the dental lamina (dots above crown of molar); reduced enamel epithelium (on surface of molar crown); rests of Malassez (dots in periodontal membrane); surface epithelium.

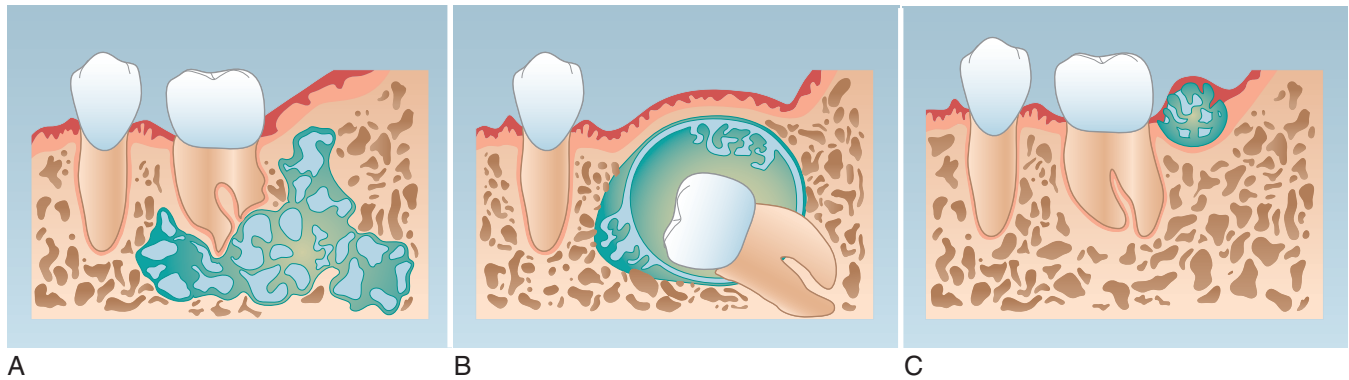
EPITHELIAL ODONTOGENIC TUMORS

AMELOBLASTOMA

AMELOBLASTOMA: A locally aggressive neoplasm of odontogenic epithelium that has a wide spectrum of histologic patterns resembling early odontogenesis.

Ameloblastoma is a benign neoplasm derived from residual epithelial components of tooth development. Its growth pattern recapitulates many of the embryonic structures and tissue that occur before hard tissue for-

mation. An ameloblastoma can arise from any of the multiple sources of odontogenic epithelium that remain within the alveolar soft tissue and bone. Four of these sources are (1) remnants of the dental lamina (rests of Serres), (2) reduced enamel epithelium, (3) rests of Malassez, and (4) the basal cell layer of overlying surface epithelium (Figure 5-3). For many years, ameloblastoma had been regarded as a single, distinct clinical entity with a broad spectrum of histologic features. The tumor is slow growing, locally aggressive, and capable of causing large facial deformities. Ameloblastomas have a high recurrence rate if they are not widely

**FIGURE 5-4**

Ameloblastoma. Three clinical subtypes. **A**, Common (polycystic). **B**, Unicystic. **C**, Peripheral (extraosseous).

and carefully excised. Metastasis is rare. Over the last 60 to 70 years nearly all metastases have occurred in patients who have had multiple or extensive surgical treatments of their lesions.

In recent years, experience has shown that not all lesions with histologic features of ameloblastoma have the same potential for destruction, recurrence, and even metastasis. As additional information is compiled, it appears that for management purposes, not all ameloblastomas require the same surgical treatment; however, a correlation of the clinical, radiographic, and histologic features of each individually encountered lesion is required to determine the clinical subtype. Although not all lesions fall neatly into the different clinical categories, many do; for these lesions, treatment can be modified to prevent unnecessarily extensive surgery. Three clinical subtypes of ameloblastomas are generally recognized for treatment purposes: (1) the common (polycystic) ameloblastoma, (2) the unicystic ameloblastoma, and (3) the rarely encountered peripheral (extraosseous) ameloblastoma (Figure 5-4).

Common Ameloblastoma

The common ameloblastoma, sometimes referred to as *simple* or *follicular ameloblastoma*, is the most prevalent form of this lesion; nearly all occur in patients over 25 years of age. Most common ameloblastomas originate *de novo*, but some may evolve from the unicystic and peripheral clinical subtypes that have remained untreated for a prolonged period.

CLINICAL FEATURES

The common form of ameloblastoma may produce extensive, even grotesque, deformities of the mandible and maxilla (Figure 5-5). It is most commonly located in the mandible, with 75% occurring in the molar and ascending ramus areas. Lesions of the maxilla are con-

**FIGURE 5-5**

Ameloblastoma. Patient with large lesion of left posterior mandible.

centrated in the molar area, where they often extend into the maxillary sinus and floor of the nose. The majority occurs in patients between 20 to 40 years of age, although they can occur at any age. No significant sex or race predilection exists. A feature of this form of ameloblastoma is the tendency to expand the bony cortices, because their slow growth allows time for the periosteum

to produce a thin shell of bone ahead of the expanding lesion. This thinned outer shell of bone cracks easily when palpated—a diagnostic sign referred to as “eggshell cracking.”

RADIOGRAPHIC FEATURES

Multiloculation characterizes the larger lesions and gives the radiograph a “soap bubble” appearance (Figure 5-6). The actual size of the lesion is usually difficult

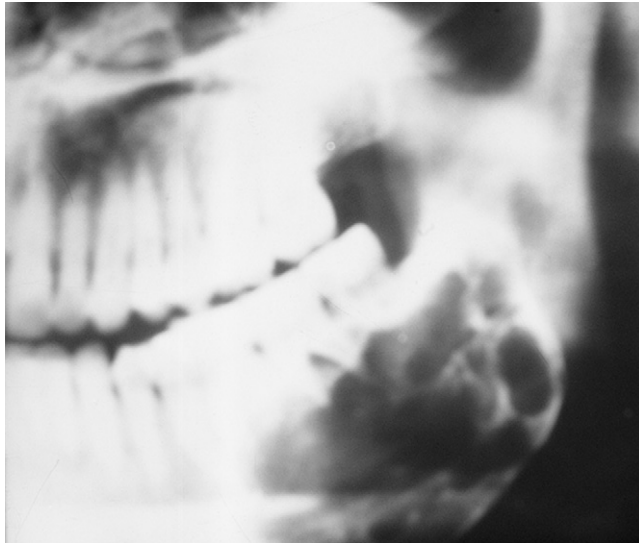


FIGURE 5-6
Ameloblastoma. Radiograph exhibiting multilocular (“soap bubble”) appearance.

to determine because lesions do not exhibit a distinct line of demarcation with the normal bone. Root resorption is uncommon but is occasionally observed in some rapidly growing lesions (Figure 5-7).

HISTOPATHOLOGY

The classic microscopic appearance of an ameloblastoma consists of epithelium in which the basal cell layer contains columnar or palisaded cells that have a tendency for the nucleus to move from the basement membrane to the opposing end of the cell, a process referred to as *reverse polarization* (Figure 5-8). The cytoplasm adjacent to the basement membrane assumes a clear zone that is reminiscent of the change that occurs in the cells of the inner enamel epithelium before they undergo transition to presecretory ameloblasts. This histologic feature is present in other odontogenic lesions, such as calcifying odontogenic cysts and odontogenic keratocysts. In ameloblastoma, the reverse polarization of the basal cell layer must be part of one of the specific architectural patterns of epithelium that is known to be associated with locally aggressive behavior. The two most common are the **follicular** and **plexiform** patterns.

The follicular pattern is the most prevalent, recapitulating the earlier stages of tooth development. It consists of epithelium in the form of islands, strands, and medullary arrangements against a background stroma of fibrous connective tissue. The epithelial arrangements have an outer border composed of the palisaded ameloblast-like cells in which reversed polarization has occurred; the remainder consists of loosely

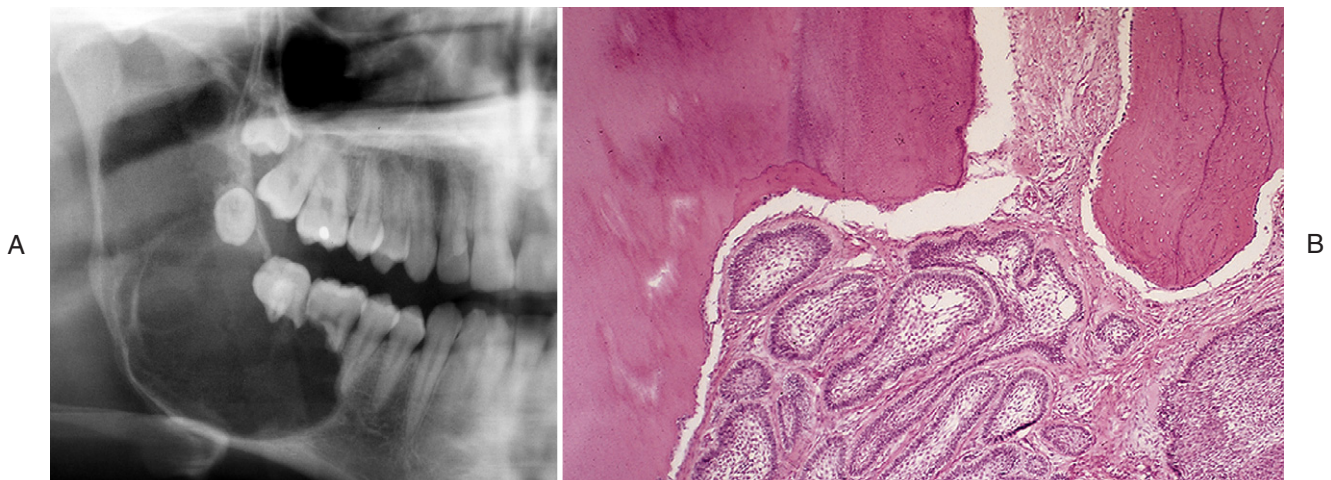


FIGURE 5-7
Ameloblastoma. **A**, Radiograph illustrating extensive polycystic lesion of right mandible extending into the coronoid process, with resorption of roots of the molars and premolar teeth. **B**, Photomicrograph of neoplastic cells in close proximity to resorbed roots of molar tooth (left side).

arranged and widely separated triangular-shaped cells that are similar to those of the stellate reticulum found in the bell stage of odontogenesis. Occasionally a distinctive zone of hyalinization surrounds the epithelial islands. This zone is believed to be an inductive effect of odontogenic epithelium on the connective tissue. In some islands the stellatelike cells of the central areas degenerate, forming central microcysts (Figure 5-9, A). Large and small cysts within the epithelium are not considered a separate histologic variant because nearly all islands contain varying degrees of cell lysis. They are probably the result of ischemic degeneration within the large islands of epithelial proliferation. In other islands the central cells are transformed to squamous cells that produce keratin within individual cells or in the form of keratin pearls. When this occurs the histologic variant is referred to as the *acanthomatous pattern* (Figure 5-9, B). The central cells less commonly appear swollen and densely packed with eosinophilic granules that are ultrastructurally considered lysosomal elements. This pattern has been termed the *granular cell variant* (Figure 5-9, C). Most patterns of ameloblastoma exhibit cyst formation, particularly when follicles become large.

The plexiform pattern differs considerably from the follicular pattern because it does not recapitulate a recognized stage of odontogenesis. It consists of epithelium that proliferates in a fishnet or mesh arrangement (Figure 5-9, D). In many areas the basal or bordering cells do not resemble ameloblasts, because they lack the distinctive reversed polarization of the nucleus. The

general pattern consists of thin strands of epithelium that are in continuity. Large and small cystlike areas are present that are not necessarily caused by the degeneration of the epithelium but are the result of the strangulation and degeneration of connective tissue stroma by the proliferating epithelium.

Other histologic variations of the common ameloblastoma are less frequently encountered. One type is the **basal cell variant**, in which only densely packed, large proliferating cuboidal-shaped basaloid cells exist in narrow strands without stellate reticulum or other forms of centrally located epithelial cells (Figure 5-10, A). Another identifiable pattern is the **desmoplastic ameloblastoma**, in which the epithelial islands and strands are small and have cuboidal and darkly stained cells. The epithelial component is widely separated by fibrous tissue that is dense and scarlike (Figure 5-10, B). This variant has a mixed radiolucent and radiopaque radiographic appearance that resembles a fibro-osseous lesion. Desmoplastic ameloblastoma is usually more difficult to treat, because it appears to have a particular predilection for penetrating the surrounding trabecular bone and remaining undetected. Consequently, finding the exact interface of the lesion with normal bone is especially difficult during surgical management.

TREATMENT

In general, all histologic variants of common ameloblastomas have similar biologic behavior and are not managed differently because of their microscopic features.

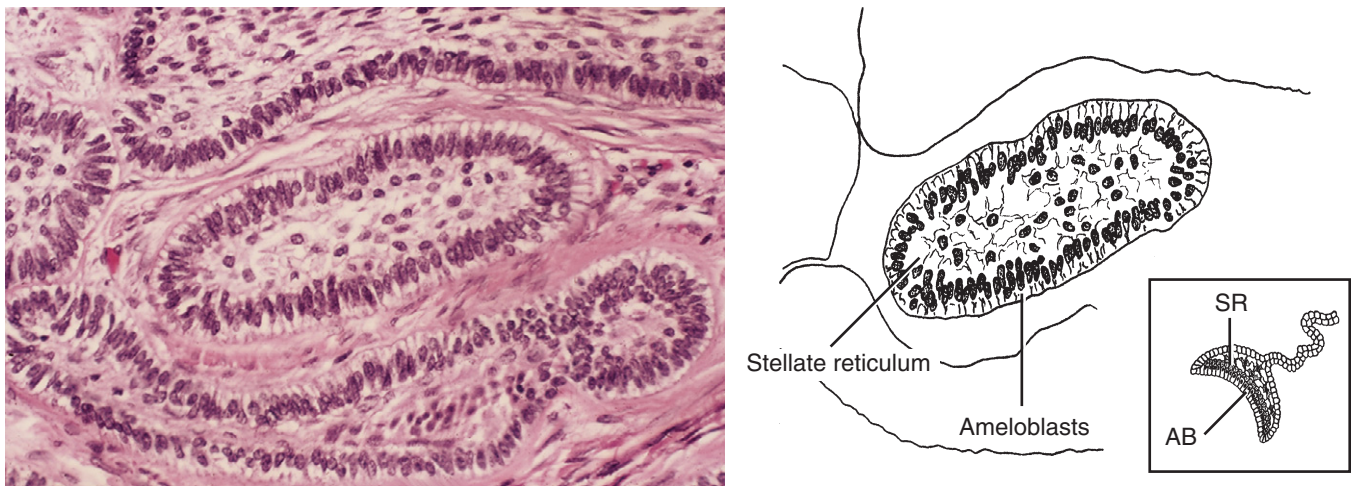
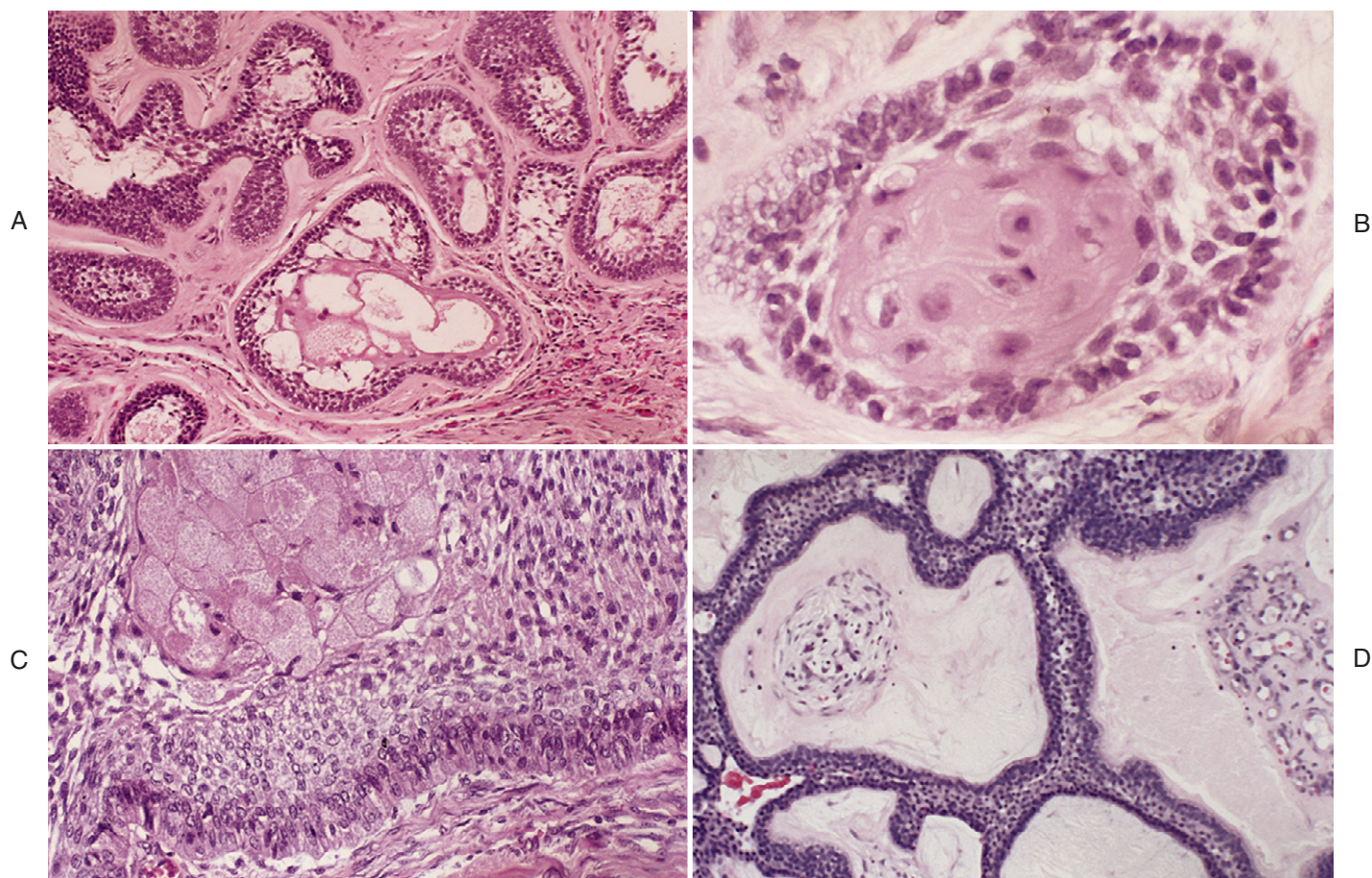
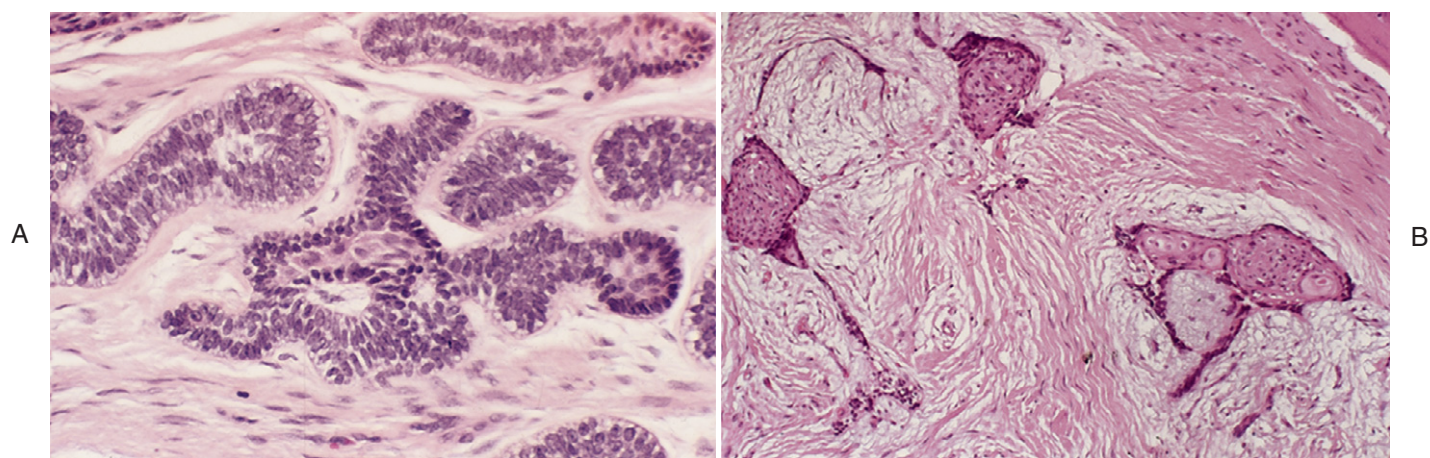


FIGURE 5-8

Ameloblastoma. Classic microscopic features of the common follicular form of ameloblastoma that demonstrate movement of the nucleus from basement membrane pole of basal cells to opposite pole (reverse polarization), resulting in outer cells resembling presecretory ameloblasts. Tumor recapitulates cap and early bell stage of odontogenesis (*inset*). AB, Ameloblasts; SR, stellate reticulum.

**FIGURE 5-9**

Ameloblastoma. Microscopic features of various histologic patterns. **A**, Follicular. **B**, Acanthomatous. **C**, Granular cell. **D**, Plexiform.

**FIGURE 5-10**

Ameloblastoma. Microscopic features of less common histologic patterns. **A**, Basal cell. **B**, Desmoplastic.

They have a propensity to penetrate the adjacent trabecular spaces of bone, without immediately causing the hard tissue to resorb; therefore radiographs and other bone-imaging techniques are not always able to delineate the lesion's boundary. The best chance of completely removing the lesion is with marginal (block) resection. Because this lesion has difficulty penetrating dense cortical bone, the inferior border of the mandible can sometimes be preserved. If the inferior border is involved, segmental resection is necessary and results in the loss of bone continuity. Hemimandibulectomy or hemimaxillectomy are nearly always required in very large lesions. All lesions are treated surgically, because they are relatively radioresistant.

Unicystic Ameloblastoma

The designation of unicystic ameloblastoma as a distinct clinical entity is a relatively new concept that has gained wide acceptance, because it provides a basis for pursuing a more conservative surgical approach to treatment of a special form of ameloblastoma. Most of these lesions are found during microscopic examination of a large unilocular cyst commonly associated with the crown of an impacted tooth in a young patient (Figure 5-11). Whether the lesion represents a transformation from a normal cystic lining or arises de novo from preexisting odontogenic epithelial remnants cannot be determined. In many lesions, areas of a normal cystic lining are adjacent to the ameloblastomatous tissue; in other lesions, normal epithelial lining cannot be found.

CLINICAL FEATURES

Lesions of unicystic ameloblastoma most commonly occur in patients who are 16 to 20 years of age; occasionally, lesions occur in younger patients. Rarely, lesions have been found in patients up to the age of 40. The peak occurrence of unicystic ameloblastoma appears to be 20 years earlier than for common ameloblastoma. With few exceptions, the unicystic ameloblastoma occurs in a dentigerous cyst relationship and is usually associated with a severely displaced third molar. In rare instances, lesions occur in the mandibular premolar area, which is the common site of lateral periodontal cysts, and others occur in the posterior mandible beyond the tooth-bearing areas. Lesions more commonly occur in the mandible than in the maxilla.

RADIOGRAPHIC FEATURES

The radiographic appearance is important in the diagnosis because it determines whether the lesion is unilocular, a necessary criterion for unicystic ameloblastoma. Lesions are usually well demarcated and may even be corticated. A tooth is often present within the radiolucency. When lesions are located in the premolar area, the roots of adjacent teeth may be displaced.

HISTOPATHOLOGY

The lesion consists of a dense, uniformly thickened, fibrous connective tissue capsule, surrounding a solitary large fluid-filled lumen. The epithelial lining of the lumen is uniform in thickness and has a slightly hyperchromatic layer of palisaded basal cells, most of which

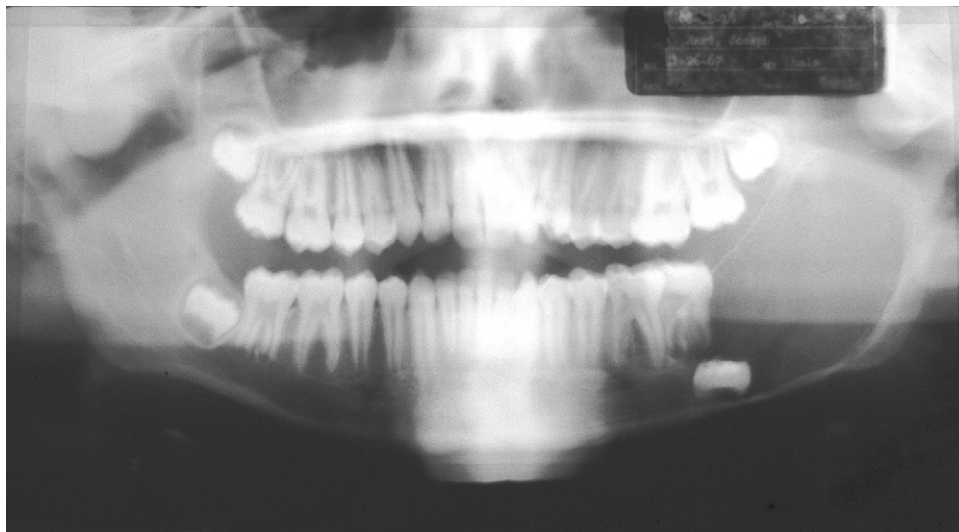


FIGURE 5-11

Unicystic ameloblastoma. Radiograph of young patient with large lesion of left mandible, exhibiting inferiorly displaced, partly formed molar and expansion of cortical plates.

exhibit reversed polarization of the nucleus. The remaining layers resemble stellate reticulum (Figure 5-12, A). Some lesions will contain areas in which the epithelium is thickened with papillary projections extending into the lumen. This histologic pattern is referred to as *intraluminal unicystic ameloblastoma* (Figure 5-12, B). When the thickened lining penetrates the adjacent capsular tissue, it is termed a *mural unicystic ameloblastoma* (Figure 5-12, C). In some dentigerous cysts a slightly different histologic pattern occurs. The pattern consists of intraluminal nodular projections that contain a network or mesh pattern of epithelium without the distinctive ameloblast-like changes of the basal cell layer. This pattern is referred to as *plexiform unicystic ameloblastoma* (Figure 5-12, D).

TREATMENT

The treatment of unicystic ameloblastoma depends on the histologic pattern. When the intraluminal or the plexiform pattern is present, enucleation is usually suf-

ficient. If the lesion contains a mural component that extends into the wall to the level of interface with the bone, marginal resection is necessary to ensure adequate removal.

Peripheral Ameloblastoma

Peripheral (extraosseous) ameloblastoma is a very uncommon odontogenic tumor that histologically resembles the intraosseous common ameloblastoma but is limited to the soft tissues of the gingiva. It is believed to arise directly from the overlying epithelium or from the remnants of the dental lamina located in the extraosseous soft tissue. Separation of this lesion from odontogenic hamartoma and peripheral odontogenic fibroma is sometimes difficult. The odontogenic hamartoma is a collection of inactive odontogenic rests, and the peripheral odontogenic fibroma is primarily a fibrous lesion containing occasional strands of odontogenic rests.

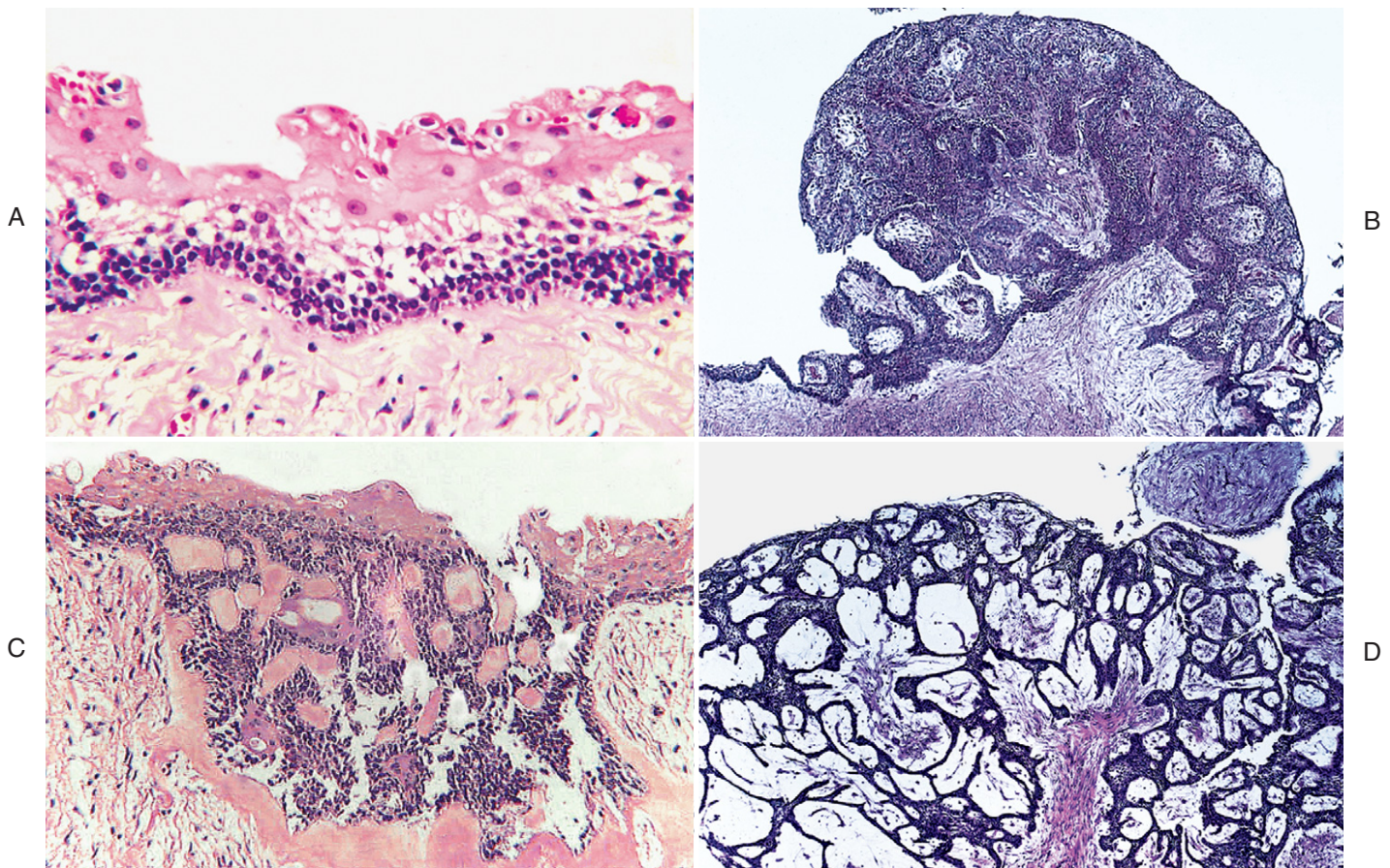


FIGURE 5-12

Unicystic ameloblastoma. Microscopic features of typical lining exhibit features of ameloblastoma (A), intraluminal papillary projection (B), intracapsular mural penetration (C), and the plexiform pattern sometimes found (D).

Peripheral ameloblastoma is easier to diagnose when the lesion exhibits the classic histologic patterns of the intraosseous common ameloblastoma and has a history of continuous growth.

CLINICAL FEATURES

Lesions usually appear as firm sessile nodules of the gingiva that range in size from 0.5 to 2.0 cm; they have a smooth surface and normal coloration. If the lesions

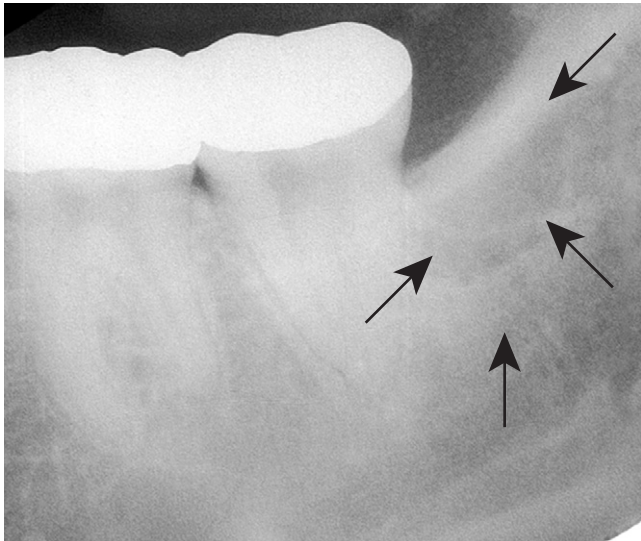


FIGURE 5-13
Peripheral ameloblastoma. Radiograph of lesion of retromolar pad exhibiting saucerization (arrows) of cortical bone.

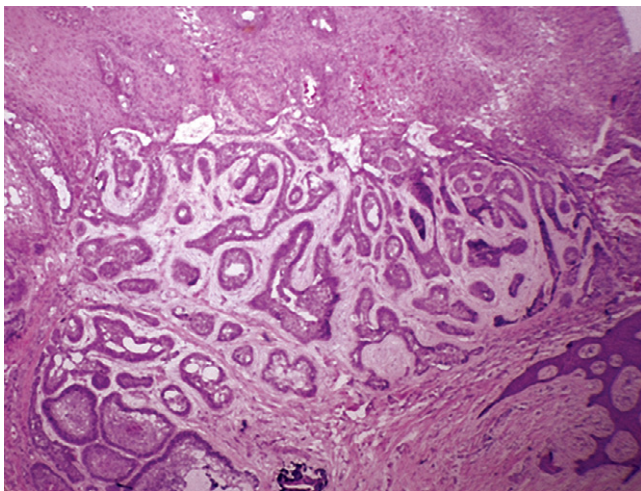


FIGURE 5-14
Peripheral ameloblastoma. Microscopic appearance exhibiting islands of follicular ameloblastoma in close proximity to surface epithelium.

originate from surface epithelium, they may be erythematous or ulcerated. Patients have been documented from 23 to 82 years of age, and lesions occur on the mandible twice as often as on the maxilla.

RADIOGRAPHIC FEATURES

Because the lesions are primarily extraosseous, bone changes are seldom present. Occasionally there will be a superficial saucerization of the cortical plate (Figure 5-13) that appears as a cup-shaped radiolucency beneath the elevated nodule as the result of the pressure the lesion exerts on the bone. If the lesion is located in the interdental papilla area, some tooth separation may occur.

HISTOPATHOLOGY

The tissue is composed of islands and strands of odontogenic epithelium, usually resembling the follicular pattern of intraosseous common ameloblastoma. The epithelial islands commonly exhibit the acanthomatous variant of this pattern, with central areas of keratin formation or the cystic pattern. In some lesions the epithelial strands are in continuity with the surface epithelium and appear to arise from this source (Figure 5-14). The epithelial islands and strands are usually surrounded by fibrous tissue. Small lesions have an inferior margin that is usually above the cortical bone. Large lesions have a pushing margin that produces a cup-shaped resorption of the cortical plate.

TREATMENT

The recommended treatment for peripheral ameloblastoma differs from the treatment of other forms of ameloblastoma because the tumor is usually small and remains localized to the superficial soft tissue. Most lesions are successfully managed with local excision that includes a small margin of normal tissue. The inferior margin should include periosteum to ensure that bone penetration has not occurred.

CALCIFYING EPITHELIAL ODONTOGENIC TUMOR

CALCIFYING EPITHELIAL ODONTOGENIC TUMOR:

A locally aggressive tumor consisting of strands and medullary patterns of squamous and clear cells that are often accompanied by spherical calcifications and amyloid-staining hyaline deposits.

The calcifying epithelial odontogenic tumor (CEOT) is frequently referred to by the eponym “Pindborg tumor.” It is rare, representing less than 1% of all odontogenic tumors. The lesion is locally aggressive with a biologic behavior similar to the common form of intraosseous ameloblastoma. It is thought to originate from the epithelial rests of the dental lamina or from the reduced

**FIGURE 5-15**

Calcifying epithelial odontogenic tumor. **A**, Panoramic radiograph of lesion of right posterior mandible that occurs as a diffuse radiolucency extending to the inferior border. Faintly visible focal radiopacities are present. **B**, Periapical radiograph exhibiting mixed radiolucent and radiopaque intraosseous lesion lacking demarcation of its boundaries. (**A** courtesy Dr. Heddie O. Sedano.)

enamel epithelium that overlies the crowns of the teeth. The neoplastic component of CEOT is reminiscent of epithelial and calcified structures normally found around the crowns of teeth. Unlike ameloblastoma, it is composed of epithelial cells that do not resemble ameloblasts, and it usually contains spherical and diffuse calcifications within the epithelial islands and the connective tissue stroma. CEOT occurs as either a central (intraosseous) or peripheral (extraosseous) lesion.

CLINICAL FEATURES

Central CEOT occurs between the ages of 20 and 60 years, with a mean age of 40. Two thirds of the lesions are in the mandible. In both jaws most lesions occur in the molar area, followed in frequency by the premolar area. The remainder of the lesions is equally distributed throughout the rest of the jaws. The tumor presents as a slowly enlarging, painless mass. Nasal airway obstruction, epistaxis, and proptosis are sometimes experienced in the maxilla.

Peripheral CEOT most commonly occurs in the anterior part of the mouth. It presents as a superficial soft tissue swelling of the gingiva in tooth-bearing and edentulous areas of the jaws.

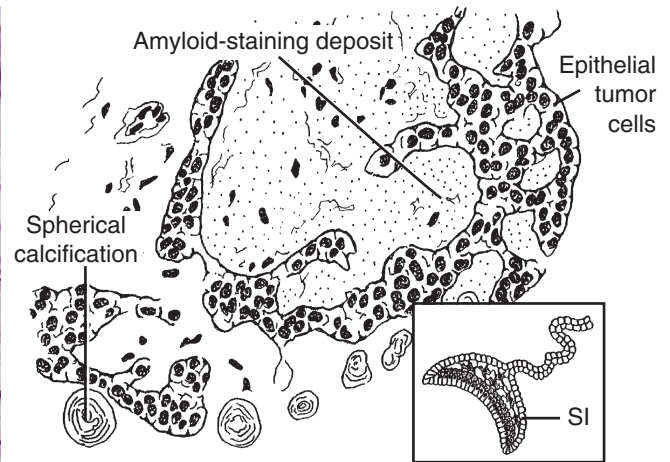
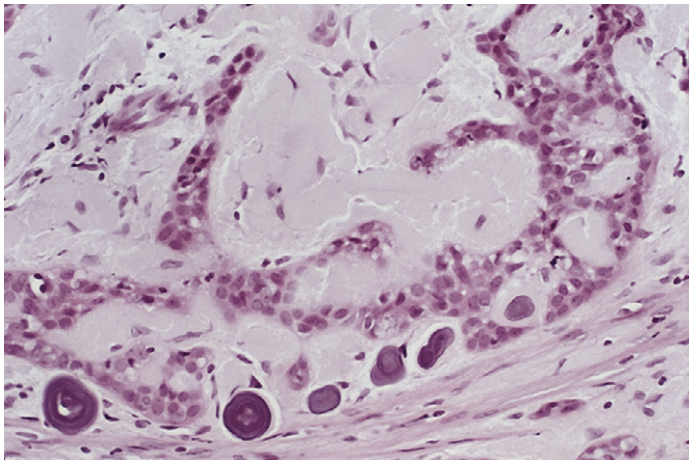
RADIOGRAPHIC FEATURES

Because calcifications are usually small, lesions tend to occur as a diffuse radiolucency with faint flecks of calcified structures (Figure 5-15, A). CEOT less commonly appears radiographically as a mixture of radiolucent and radiopaque areas (Figure 5-15, B). The radiopaque areas can be diffuse and faint or discrete, round structures. Intraosseous lesions may occur over teeth that are unerupted, displaced, or both. Small lesions are often unilocular radiolucencies. Similar to common ameloblastoma, lesions have indistinct lines of demarcation with the surrounding bone.

Because CEOT usually occurs over unerupted teeth and may be a radiolucent or mixed unilocular lesion, the radiographic differential diagnosis of CEOT includes dentigerous cyst, adenomatoid odontogenic tumor, and ameloblastic fibro-odontoma. The peripheral lesions are commonly radiolucent. Sometimes lesions exhibit superficial cortical erosion.

HISTOPATHOLOGY

The tumor exhibits considerable variation in its histologic appearance. The most common histologic pattern consists of sheets of polyhedral cells with prominent

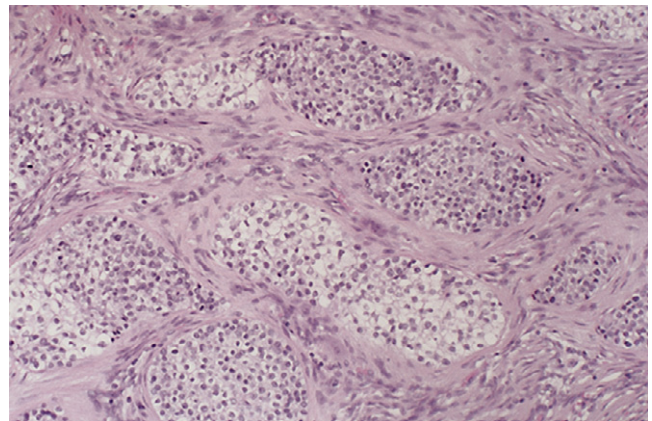
**FIGURE 5-16**

Calcifying epithelial odontogenic tumor. Characteristic microscopic features of sheets and strands of polyhedral epithelial cells, homogeneous eosinophilic deposits that stain positive for amyloid, and spherical calcifications. Tumor cells recapitulate stratum intermedium layer of the early bell stage of odontogenesis (*inset*). *SI*, Stratum intermedium.

intercellular bridges. The cells may exhibit pleomorphism, multinucleation, prominent nucleoli, and occasionally hyperchromatism. Although these cells may have an atypical appearance, mitotic figures are rarely found. In addition to spherical calcifications, pools of homogeneous eosinophilic material are often found within and between the sheets of epithelial cells (Figure 5-16). The spherical calcifications are scattered throughout the epithelium and connective tissue; proportions vary considerably among lesions. Lesions also contain varying proportions of epithelial cells with a clear cytoplasm. When clear cells dominate the epithelial component, the lesion is referred to as *clear cell variant* of CEOT (Figure 5-17). This is a particularly common histologic feature of peripheral lesions. Peripheral lesions have less tendency to develop calcifications. The nature of the eosinophilic deposits has been controversial. Because the substance is often positive with amyloid stains such as Congo red or thioflavine T, it is believed to be a form of amyloid. Other interpretations are that the deposits are aberrant forms of tissue degeneration, type IV collagen and basal lamina, enamel matrix, or keratin.

TREATMENT

Because of the sparse number of cases with long-term follow up, the biologic behavior of CEOT is not well understood. The lesion is locally invasive and without capsule formation. Because a few recent cases with multiple occurrences exhibited malignant features, resection that includes a margin of normal soft tissue or bone is recommended.

**FIGURE 5-17**

Calcifying epithelial odontogenic tumor. Characteristic microscopic features of the clear cell variant exhibiting lobular patterns of clear cells and eosinophilic cells. This variant has less tendency for formation of spherical calcifications and amyloid-staining hyaline deposits.

ADENOMATOID ODONTOGENIC TUMOR

ADENOMATOID ODONTOGENIC TUMOR: A well-circumscribed lesion derived from odontogenic epithelium that usually occurs around the crowns of unerupted anterior teeth of young patients and consists of epithelium in swirls and ductal patterns interspersed with spherical calcifications.

The adenomatoid odontogenic tumor (AOT) is sometimes referred to as *odontogenic adenomatoid tumor*. Its name reflects the characteristic histologic feature of duct-like structures interspersed throughout the epithelial component, giving the lesion a glandular or adenomatous appearance. Its usual clinical location around the crown of a tooth, combined with the findings of ultrastructural and histochemical studies, suggests that the lesion probably originates from the reduced enamel epithelium of the

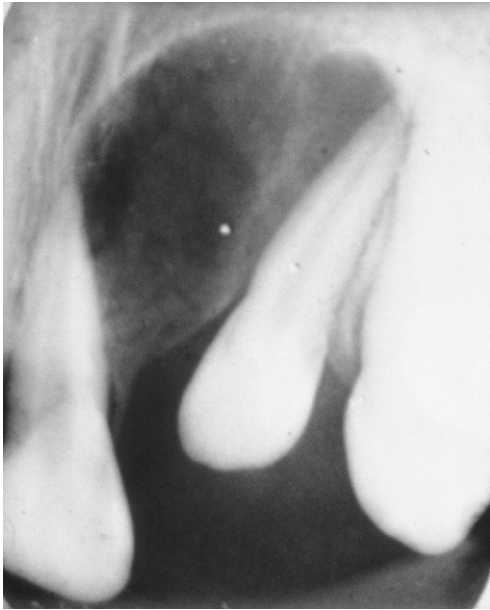


FIGURE 5-18
Adenomatoid odontogenic tumor. Radiograph demonstrating a well-demarcated mixed radiolucent and radiopaque lesion surrounding an impacted maxillary lateral incisor.

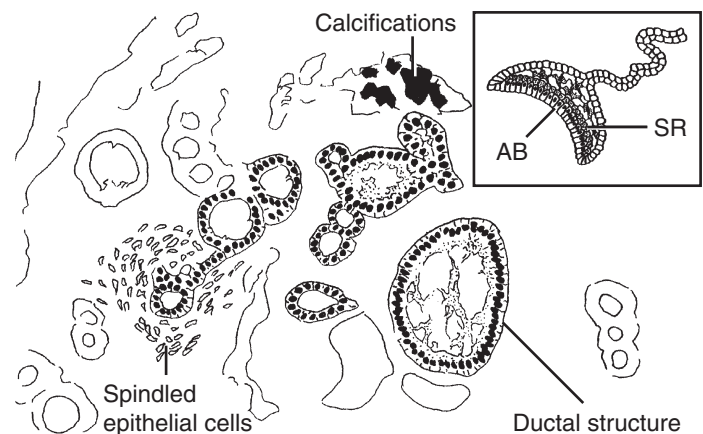
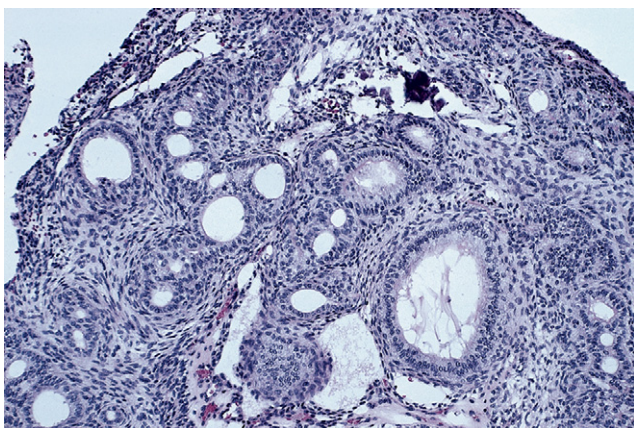


FIGURE 5-19
Adenomatoid odontogenic tumor. Microscopic features reveal the nodular pattern of spindled cells, ductal structures, and a focal area of calcification (*upper center*), which is characteristic of this lesion. Tumor cells recapitulate presecretory ameloblasts and stellate reticulum of the cap and early bell stage of odontogenesis (*inset*). AB, Ameloblasts; SR, stellate reticulum.

postsecretory phase of enamel organ development. Because the lesion is biologically nonaggressive and requires conservative treatment, its recognition and differentiation from the other epithelial odontogenic lesions, particularly ameloblastoma, is of utmost importance.

CLINICAL FEATURES

The AOT is usually associated with an impacted tooth and is often a cause of failure of the tooth to erupt. The lesion occurs during the second decade of life, commonly in patients 14 to 15 years of age; females are affected more frequently than males. It most often occurs in the anterior mouth, usually around an impacted cuspid. Occasionally these lesions have been associated with other teeth, including molars. The common presentation is in a patient who exhibits an area of swelling over an unerupted tooth.

RADIOGRAPHIC FEATURES

The radiographic appearance of AOT is usually as a unilocular lesion with well-corticated borders that contains a tooth. Most lesions are radiolucent, but some contain faint flecks of radiopacities. Lesions often surround the crown of an impacted tooth, as they do in a dentigerous cyst. However, close examination reveals that AOT differs from a dentigerous cyst, because the radiolucency usually extends apically beyond the cemento-enamel junction (Figure 5-18).

HISTOPATHOLOGY

AOT is composed of an outer capsule of fibrous connective tissue surrounding a nodular pattern of epithelial cells. The rest of the tissue may be solid or contain focal cystic areas. The nodules are composed of spindled epithelial cells that are often in a swirled pattern.

Scattered throughout most lesions are ductal structures composed of a circular arrangement of columnar cells with interposed deposits of periodic acid-Schiff (PAS)-positive eosinophilic material (Figure 5-19). This is considered a form of basement membrane. Spherical calcifications are often scattered throughout the epithelium but are not a consistent finding. The stroma may occasionally contain diffuse areas of hyaline material.

TREATMENT

AOT is successfully treated with curettage and usually requires the removal of associated teeth. Recurrences are rare.

CALCIFYING ODONTOGENIC CYST

CALCIFYING ODONTOGENIC CYST: A rare, well-circumscribed, solid or cystic lesion derived from odontogenic epithelium that microscopically resembles ameloblastoma but differs by containing ghost cells and spherical calcifications.

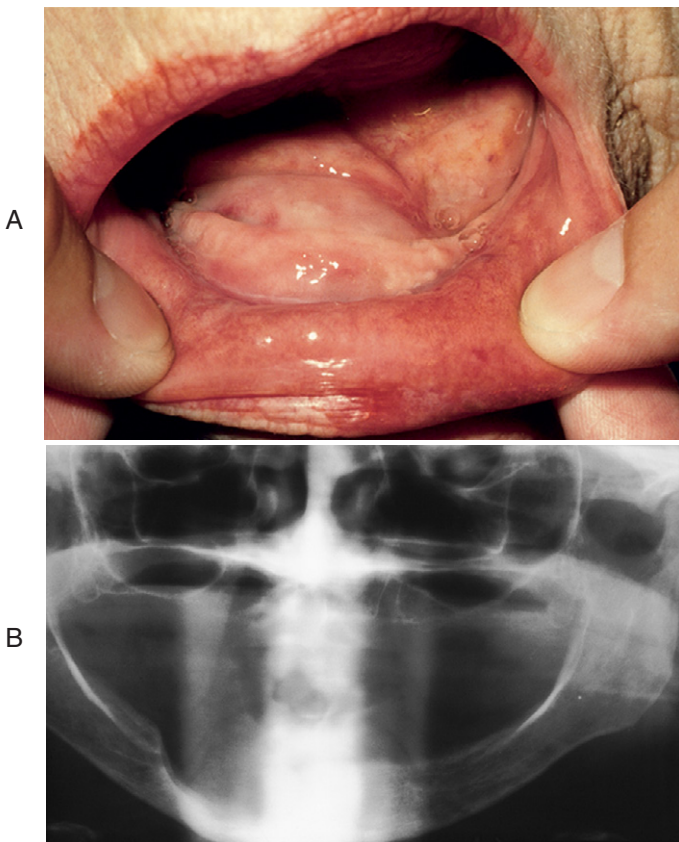


FIGURE 5-20

Calcifying odontogenic cyst. **A**, Patient exhibits extensive buccal and lingual expansion of the cortical plates of the right mandible. **B**, Radiograph of same patient that demonstrates a large radiolucent cup-shaped defect of the anterior right mandible with sharp line of demarcation with surrounding bone.

The calcifying odontogenic cyst (COC) is an uncommon odontogenic lesion with a somewhat wide spectrum of histologic features. Because the lesion sometimes appears as a solid noncystic lesion, referred to as *odontogenic ghost cell tumor*, it is no longer classified as one of the odontogenic cysts. In addition to its purely cystic and solid forms, COC may be associated with an odontoma.

CLINICAL FEATURES

The COC and its solid counterpart, the odontogenic ghost cell tumor, can occur in any part of the tooth-bearing areas of the mouth. It is somewhat more common in the areas anterior to the first molar. Lesions occur at any age but have a predilection for patients in the second decade and may occur in an extraosseous or intraosseous location. Extraosseous lesions appear as focal localized swellings, whereas intraosseous lesions produce a generalized expansion of the buccal and lingual cortices (Figure 5-20, A). Pain is usually absent.

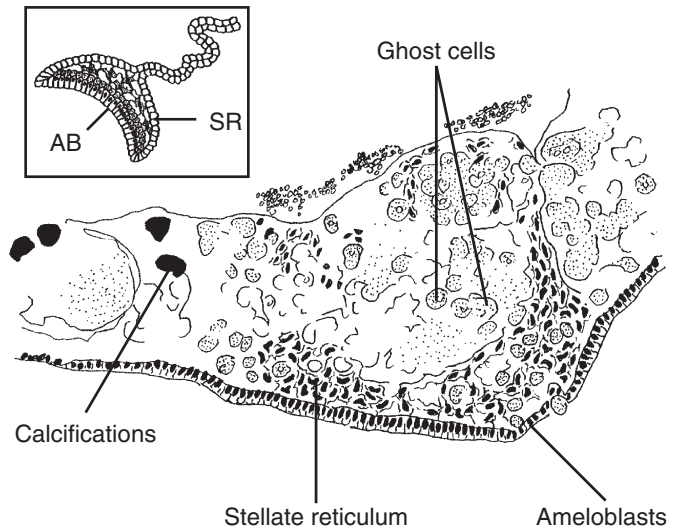
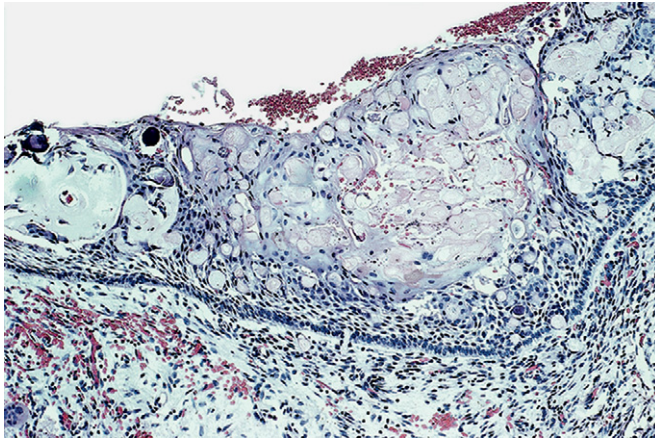
RADIOGRAPHIC FEATURES

Lesions most commonly appear as well-circumscribed unilocular radiolucencies (Figure 5-20, B) containing flecks of indistinct radiopacities. In some lesions the flecks and small nodular radiopacities are confined to the periphery, with larger toothlike structures more centrally located (Figure 5-21). In younger patients, lesions may closely resemble a developing odontoma or ameloblastic fibro-odontoma.



FIGURE 5-21

Calcifying odontogenic cyst. Radiograph of large lesion of maxilla with odontoma included within the lesion.

**FIGURE 5-22**

Calcifying odontogenic cyst. Microscopic features reveal a thick epithelial layer lining a cystic space consisting of palisaded columnar basal cells, accumulations of enlarged eosinophilic epithelial cells without nuclei (ghost cells), and spherical calcifications. Tumor cells recapitulate the early bell stage of odontogenesis (*inset*). AB, Ameloblasts; SR, stellate reticulum.

HISTOPATHOLOGY

The microscopic appearance of COC varies. Some lesions have a cystic center, and others are solid. The epithelial component resembles that found in ameloblastoma and is common to all lesions. The epithelial component consists of an outer layer of palisaded columnar basal cells and an inner layer reminiscent of stellate reticulum.

Greatly enlarged eosinophilic epithelial cells without visible nuclei, referred to as *ghost cells*, are present within the stellate reticulum-like areas. Multiple spherical and diffuse calcifications within the epithelium and connective tissue are also included (Figure 5-22). In some COCs the ameloblastomatous epithelium may extend into the capsular wall. Linear deposits of hyalinized material are located within the connective tissue beneath the epithelium.

TREATMENT

Most lesions of COC require conservative treatment. Peripheral tumors are usually treated with simple excision. Central tumors generally respond to enucleation, and recurrences are uncommon. The solid form of the tumor (ghost cell odontogenic tumor) is usually amenable to curettage or simple excision; however, on occasion it can be more aggressive and require block or partial resection.

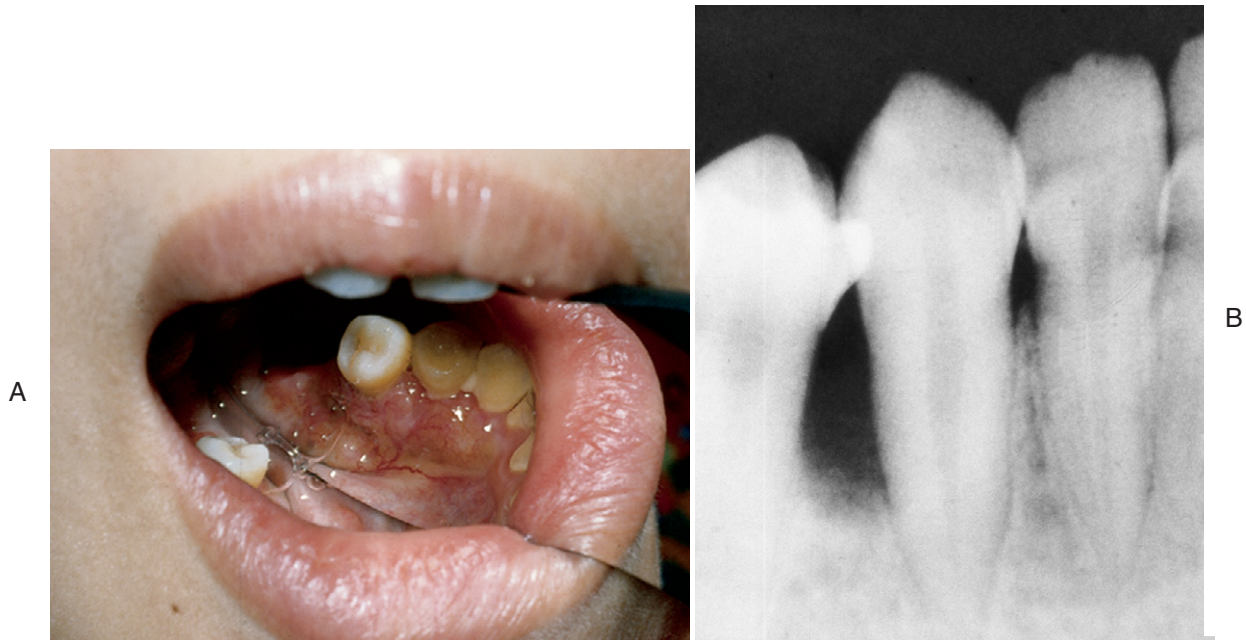
SQUAMOUS ODONTOGENIC TUMOR

SQUAMOUS ODONTOGENIC TUMOR: A rare, sometimes multifocal, potentially aggressive lesion derived from odontogenic epithelium and consisting of islands of stratified squamous epithelium that commonly contain microcysts and calcifications in a dense fibrous background.

The squamous odontogenic tumor (SOT) was first described in 1975. Its inclusion as a separate entity in a classification of odontogenic tumors is based on its characteristic histologic features and distinct biologic activity. The cases reported and the experiences of some clinicians resulted in the expansion of the original description of SOT. The available information seems to indicate that the lesion can be multifocal and have a somewhat aggressive potential if not treated in its early stages. SOT may originate from the remnants of the dental lamina, rests of Malassez, or overlying epithelium.

CLINICAL FEATURES

Lesions of SOT usually occur anterior to the molars and are equally distributed between the mandible and maxilla. Lesions occur in patients at any age, with a peak incidence in the third decade. Lesions are first detected as either a painless swelling or as looseness

**FIGURE 5-23**

Squamous odontogenic tumor. **A**, Patient with multiple small nodules on lingual gingiva in mandibular premolar area. **B**, Radiograph of same patient that reveals loss of interproximal alveolar bone.

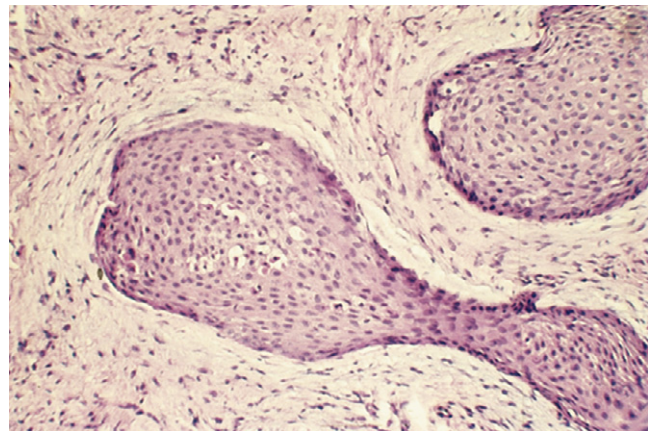
of teeth in a region (Figure 5-23, A). Initially the lesions are slow growing, and patients indicate that the swelling or mild symptoms have been present for 1 or more years.

RADIOGRAPHIC FEATURES

Small lesions appear as unilocular radiolucencies (Figure 5-23, B), whereas large ones are multilocular and have an indistinct border. Tooth separation is common with smaller lesions when they are located in the bone that is coronal to the root apices. Resorption of roots is usually absent.

HISTOPATHOLOGY

Lesions of SOT consist of rounded and elongated islands of relatively normal-appearing stratified squamous epithelium against a cellular fibrous connective tissue background. The epithelial islands vary in size and have a basal cell layer of inactive-appearing cuboidal cells. The remainder of the islands is composed of matured intermediate cells with prominent desmosomal bridges (Figure 5-24). Many of the epithelial islands have central areas of microcyst formation, whereas others contain spherical or irregularly shaped calcified structures. Similar calcifications can also be found in the connective tissue stroma.

**FIGURE 5-24**

Squamous odontogenic tumor. Microscopic features reveal a background of cellular fibrous connective tissue containing multiple islands of inactive-appearing squamous epithelium with central areas exhibiting a tendency to become cystic.

TREATMENT

Most small lesions can be controlled with local curettage; large lesions require block resection.

CONNECTIVE TISSUE ODONTOGENIC TUMORS

ODONTOGENIC FIBROMA

ODONTOGENIC FIBROMA: *A peripheral or intraosseous (central) benign neoplasm derived from connective tissue of odontogenic origin containing widely scattered islands and strands of embryonic odontogenic epithelium and calcifications.*

The concept of odontogenic fibroma is presently in transition. Originally the name was applied to any intraosseous tumor composed predominantly of fibrous connective tissue that was located within the tooth-bearing areas of the jaws. Some of these lesions were relatively acellular and were composed of dense bundles of collagen in a fascicular pattern with few spindled fibroblasts. Others were composed of a mixture of acellular connective tissue that contained islands and strands of odontogenic epithelium surrounded by zones of myxomatous tissue, hyalin deposits, and calcifications. The latter lesion (containing odontogenic epithelium) was featured in the *World Health Organization Classification of Odontogenic Tumors* as an example of a true odontogenic fibroma. The former lesion (without odontogenic epithelium) is presently considered an intraosseous form of desmoplastic fibroma. Both intraosseous forms of odontogenic fibroma are rare; the peripheral lesion is relatively common.

Peripheral Odontogenic Fibroma

The peripheral odontogenic fibroma is the most common form of odontogenic fibroma and appears to be derived from the overlying gingival epithelium or the rests

of the dental lamina remaining in an extraosseous location. The epithelial component resembles the dental lamina formed during the early stages of odontogenesis. The lesion provides some evidence that it originates from a recapitulation of dental lamina, because the epithelium is capable of producing inductive changes in the connective tissue that are similar to changes in the dental lamina during odontogenesis.

Differentiation of this lesion from a gingival hamartoma or a peripheral ameloblastoma is often required and is usually done by evaluating the epithelial element.

CLINICAL FEATURES

The peripheral odontogenic fibroma has a similar appearance to other focal growths of the gingiva, such as peripheral fibroma (with or without ossification). It may be of normal coloration or erythematous when ulceration occurs (Figure 5-25). Interdental lesions often cause tooth separation.

RADIOGRAPHIC FEATURES

Because small lesions are located in the gingival soft tissue, radiographic alteration of the bone is not usually apparent. When lesions contain numerous calcifications within the cellular connective tissue, some small radiopaque flecks may be visible. Large lesions may reveal saucerization of the cortical bone or some widening of the cervical portion of the periodontal space.

HISTOPATHOLOGY

The lesion is composed of a mixture of somewhat dense connective tissue that separates localized zones of myxomatous or loose connective tissue. Small epithelial islands can be found near the surface adjacent



FIGURE 5-25
Peripheral odontogenic fibroma. The lesion of the mandibular buccal gingiva is raised and firm and has an erythematous surface caused by chronic irritation.

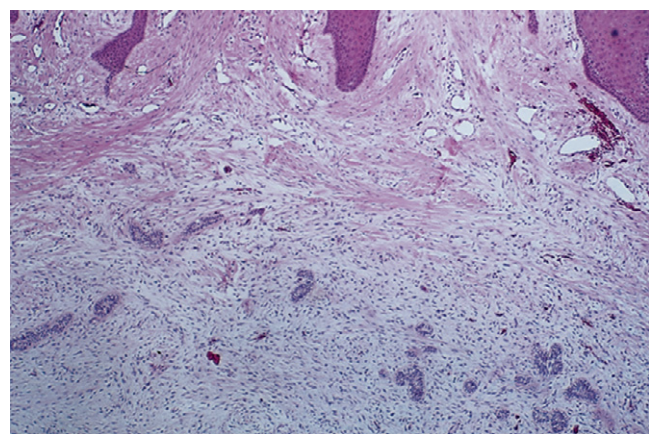


FIGURE 5-26
Peripheral odontogenic fibroma. Photomicrograph reveals a fibrous lesion containing multiple small islands and strands of odontogenic epithelium resembling remnants of the dental lamina. The connective tissue immediately adjacent to the epithelial islands is less dense and myxomatous.

to thin, elongated rete pegs and in the deep areas of myxomatous change (Figure 5-26). In these areas they are located adjacent to irregularly shaped hyalinized deposits, many of which have undergone some degree of mineralization. The epithelial islands will often contain clear cells.

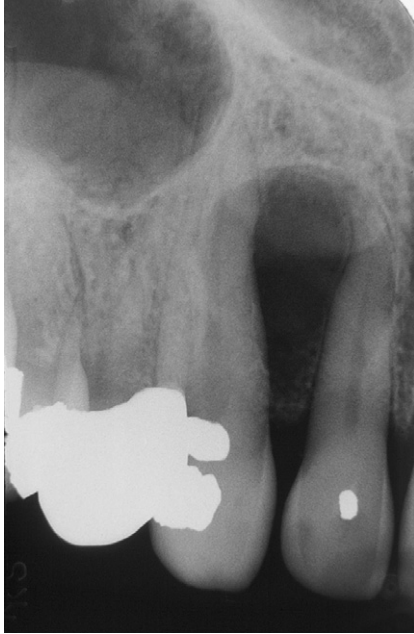


FIGURE 5-27
Central odontogenic fibroma (WHO type). Radiograph of an intraosseous lesion in the anterior maxilla exhibiting a circumscribed radiolucency.

TREATMENT

Although local excision is the treatment of choice, attempts to superficially remove the lesion without extending the deep margin to the underlying bone or into the periodontal ligament often results in recurrence.

Central Odontogenic Fibroma

The central odontogenic fibroma is a relatively uncommon odontogenic tumor that is described in the *World Health Organization Classification of Odontogenic Tumors*. Before that time, lesions with the specific histologic features ascribed to this tumor were likely diagnosed as either atypical forms of CEOT, ameloblastoma, or cementifying fibroma, depending on the amount of epithelial and calcifying elements present.

CLINICAL FEATURES

Lesions are usually asymptomatic, painless swellings commonly located in the mandible.

RADIOGRAPHIC FEATURES

The radiographic appearance is that of a nonspecific radiolucency that is unilocular and well circumscribed in some (Figure 5-27) and multilocular in others. Some faint radiopaque flecks are sometimes observed.

HISTOPATHOLOGY

The central odontogenic fibroma is composed of a cellular connective tissue that contains widely scattered thin strands of odontogenic epithelium (Figure 5-28). The epithelial component closely resembles dental

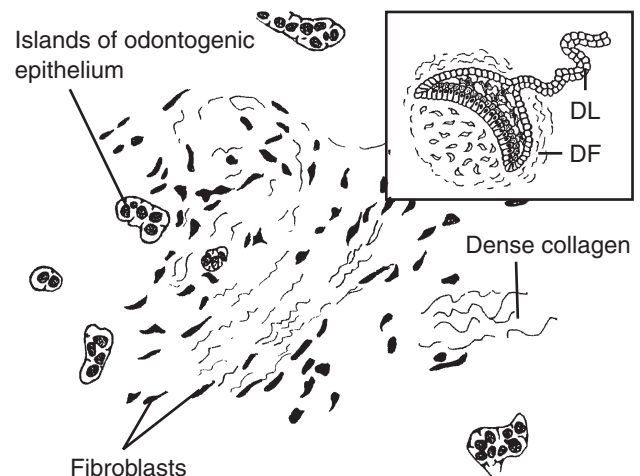
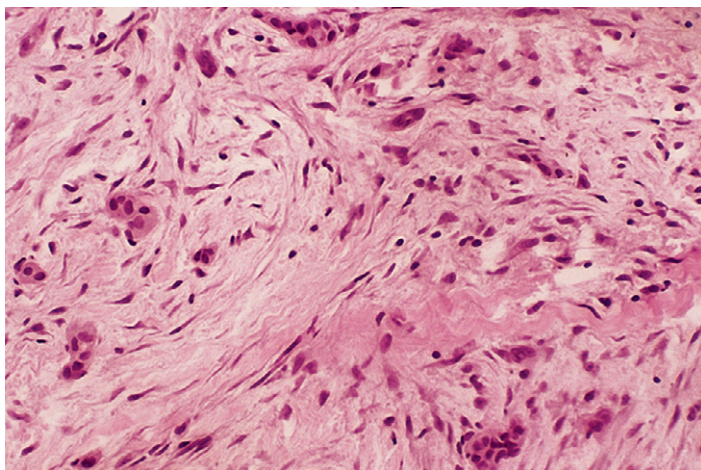


FIGURE 5-28
Central odontogenic fibroma (WHO type). Microscopic features consist of a cellular fibrous connective tissue containing multiple small islands and strands of odontogenic epithelium. Tumor recapitulates cells of dental follicle and dental lamina of the early stages of odontogenesis (*inset*). *DF*, Dental follicle; *DL*, dental lamina.

lamina and often contains cells with clear cytoplasm. Some lesions will contain varying amounts of spherical and diffuse calcifications that are usually associated with the odontogenic epithelial strands. Recently there have been several cases in which central odontogenic fibroma contained histologic components of central giant cell lesions. The significance of this finding is not known.

TREATMENT

The number of reported cases of odontogenic fibroma described by the World Health Organization (WHO) is still small, making accurate prognoses unreliable. Most cases have responded to conservative treatments such as curettage, and reports indicate that lesions separate from the surrounding bone with ease. There have been some recurrences after several years.

ODONTOGENIC MYXOMA

ODONTOGENIC MYXOMA: *An aggressive intraosseous lesion derived from embryonic connective tissue associated with odontogenesis and primarily consisting of a mucoid ground substance with widely scattered undifferentiated spindled mesenchymal cells.*

The odontogenic myxoma is an uncommon intraosseous lesion that has a distinct histologic appear-

ance and a locally aggressive behavior. It has aroused considerable interest, with a few exceptions, as have nearly all lesions found in the jaws. Occasionally, lesions have been found in the ramus and other non-tooth-bearing areas of the jaws and in other facial bones. Additionally, lesions with identical histologic features are found in the soft tissues. Studies have been undertaken on the jaw lesions in an effort to prove an odontogenic origin. This effort has been somewhat unsuccessful.

CLINICAL FEATURES

Lesions are nearly equally distributed between the mandible and maxilla. Maxillary lesions occur equally in all areas and frequently erode into the sinus, often crossing the midline and into the opposing sinus cavity. Mandibular lesions are most commonly found in the molar and premolar areas and often extend into the ramus.

Most lesions are painless, slowly enlarging swellings of the involved bone that sometimes displaces teeth. Patients are often aware of these lesions for several years before seeking attention.

RADIOGRAPHIC FEATURES

The large lesions have a somewhat distinct radiographic appearance consisting of a multilocular radiolucency with a “soap bubble” or “honeycomb” pattern (Figure 5-29, A).



FIGURE 5-29

Odontogenic myxoma. **A,** Panoramic radiograph of posterior mandible and ramus exhibiting the characteristic “honeycomb” pattern, indistinct radiolucency, faint residual fragments of trabecular bone, and expansion of cortical plates. **B,** Periapical radiograph of anterior mandible revealing a mottled radiolucency with indistinct margins and containing wisps of residual bone.

In some areas coarse or angular-shaped trabeculations are noted. In general the radiographic appearance resembles that of common melioblastoma—diffuse without a distinct demarcation with uninvolved bone. Root resorption is not a feature of myxoma, although some tooth displacement occurs (Figure 5-29, B). Small lesions are often unilocular and appear as nonspecific radiolucencies.

HISTOPATHOLOGY

The microscopic appearance of an odontogenic myxoma consists of widely separated spindle- or angular-shaped cells against a background of a mucoid, non-fibrillar ground substance (Figure 5-30). In some odontogenic myxomas, focal areas of fine strands of collagen and blood vessels exhibiting a thin outer zone of hyalinization are found. In the periphery the myxomatous tissue penetrates the trabecular spaces, producing islands of residual bone. This feature accounts for the difficulty in conservatively removing the lesion. Islands of odontogenic epithelium and focal calcifications have been observed.

Occasionally, lesions have been observed containing large amounts of a mature cellular fibrous tissue. These lesions are referred to as *myxofibroma*.

TREATMENT

Some small unilocular lesions have been treated successfully with local curettage followed by chemical cautery of the bony walls, but most lesions require block resection. Because of the gelatinous nature of the lesion, it is important to remove an intact specimen to reduce the chances of recurrence.

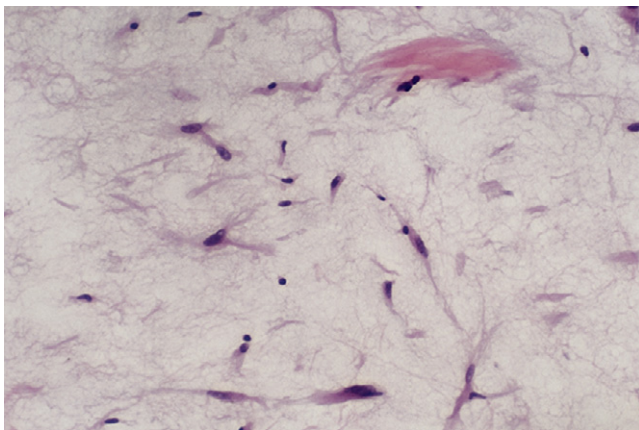


FIGURE 5-30

Odontogenic myxoma. Microscopic features reveal a background of mucoid ground substance containing widely separated spindle-shaped mesenchymal cells and occasional strands of collagen.

CEMENTOBLASTOMA

CEMENTOBLASTOMA: *A benign, well-circumscribed neoplasm of cementum-like tissue growing in continuity with the apical cemental layer of a molar or premolar that produces expansion of cortical plates and pain.*

Some lesions, such as periapical cemental dysplasia and cementifying fibroma (formerly included under the classification of odontogenic tumors), have recently been reclassified by the WHO and are discussed in Chapter 4. Cementoblastoma remains classified as an odontogenic tumor because it is considered a true benign neoplasm of cementoblasts. Although its histologic features are remarkably similar to osteoblastoma and osteoid osteoma, its growth pattern is in continuity with the cemental layer of the apical third of a tooth. Additional evidence that it is of tooth tissue origin is the continuation of the periodontal membrane around the periphery of the mass separating it from the surrounding normal bone.

CLINICAL FEATURES

The cementoblastoma is an uncommon lesion occurring in the second and third decades of life, with a peak incidence around 19 years. Nearly all tumors occur in the molar and premolar area, with lesions attached to the apical third of one of the roots. The lesions grow as true neoplasms, uniformly expanding both the buccal and lingual cortical plates. The cementoblastoma is distinctive among odontogenic tumors, because in nearly all cases patients complain of pain that becomes more intense if the area is palpated. The teeth usually remain vital.

RADIOGRAPHIC FEATURES

Lesions are unilocular and well demarcated. They may be completely radiolucent, a mixture of radiolucent and radiopaque, or completely radiopaque. Nonradiolucent lesions exhibit a peripheral zone of radiolucency continuous with the normal periodontal ligament space of the unaffected areas of the tooth. Roots adjacent to the expanding lesion often exhibit resorption of their apical third.

HISTOPATHOLOGY

The lesion is characterized by a deposition of unmineralized eosinophilic matrix rimmed by plump cementoblasts that are continuous with the normal cementum layer of one of the tooth roots (Figure 5-31). The periodontal ligament that is adjacent to the normal cementum follows the bulbous periphery of the lesion, becoming integrated with the capsular fibrous tissue that separates it from the normal bone. The peripheral zone of the lesion is relatively acellular (Figure 5-32, A), whereas the central zone is composed of

more mineralized tissue with intervening areas of soft tissue that is loose, very cellular, and exhibits an increase in vascularity. Multinucleated cells are abundant in the cellular central areas and are associated with active resorption. The mineralized tissue exhibits increased numbers of reversal lines, which is indicative of extensive remodeling during the growth of the lesion (Figure 5-32, B). The root of the involved normal tooth sometimes extends to the center of the lesion,

and the neoplastic cemental tissue is continuous with the normal cemental layer.

TREATMENT

Regardless of size, treatment of the lesion requires removal of the associated tooth. Because this lesion is well encapsulated, enucleation of the lesion from its bony crypt is usually easily accomplished. Recurrences have not been reported.

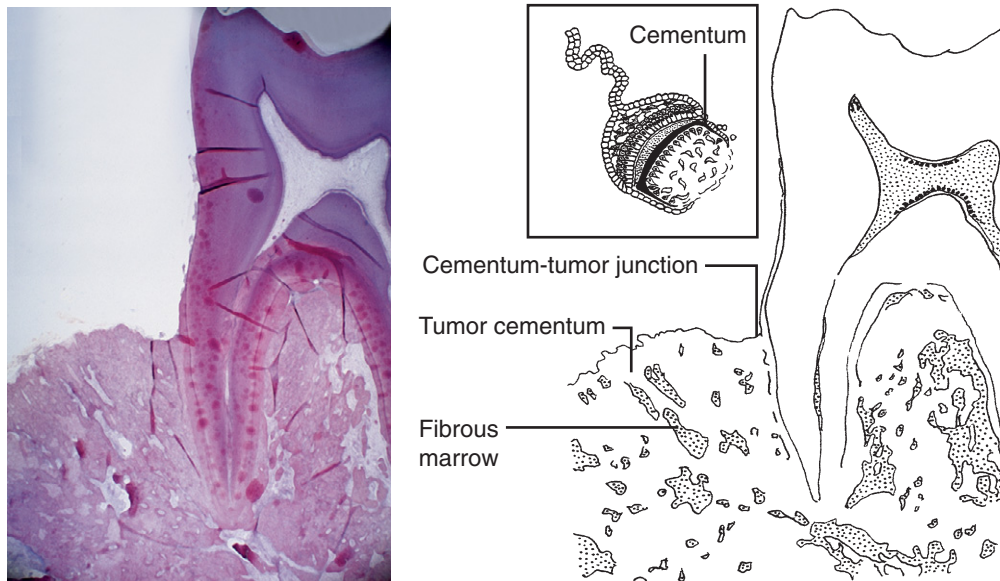


FIGURE 5-31

Cementoblastoma. Photomicrograph of a molar in which the cemental tissue of the lesion is continuous with the normal cementum of the root. Tumor recapitulates cementum deposition during root formation in the late stage of odontogenesis (*inset*).

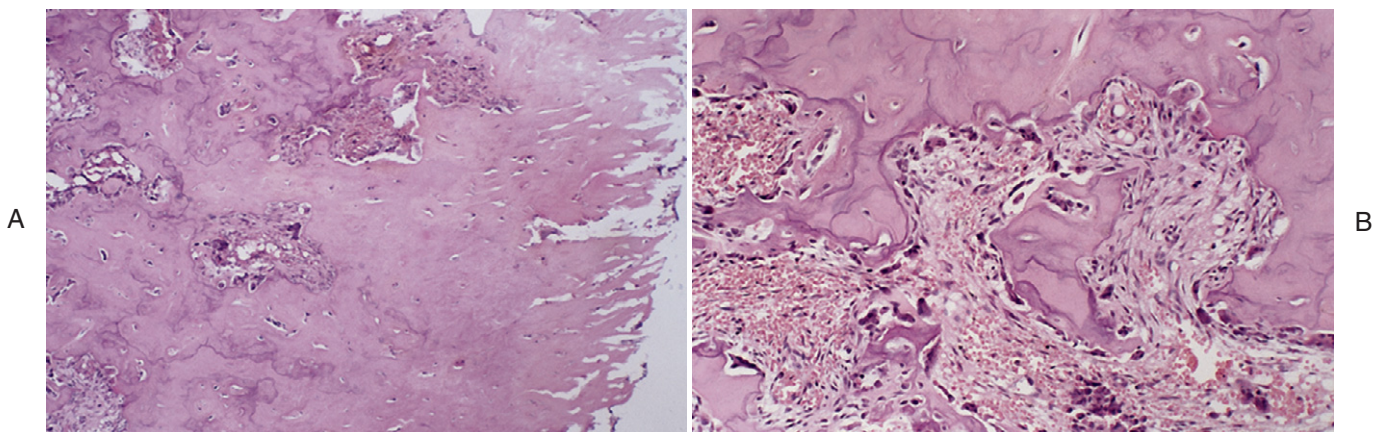


FIGURE 5-32

Cementoblastoma. Microscopic features of periphery exhibiting wide zone of hyalinized matrix (cementoid) (A) and central area of increased activity of osteoblasts and osteoclasts in cellular fibrous connective tissue (B).

MIXED ODONTOGENIC TUMORS

Mixed odontogenic tumors contain a combination of the epithelial and connective tissue elements found in all stages of odontogenesis. In the ameloblastic fibroma, the two tissue components represent an early stage of odontogenesis, before the formation of the calcified structures of enamel and dentin. The odontoma represents the opposing end stage of odontogenesis, containing primarily mature enamel, dentin, and pulp. An intermediate lesion (ameloblastic fibro-odontoma) exists, in which the tissues of all stages of odontogenesis are represented.

AMELOBLASTIC FIBROMA

AMELOBLASTIC FIBROMA: *A circumscribed lesion predominantly located over unerupted molars in young patients; the epithelium and connective tissue recapitulate the cap and bell stages of odontogenesis.*

The ameloblastic fibroma is a true histologic biphasic tumor because the epithelial and mesenchymal components are part of the neoplastic process. Questions have arisen regarding the exact nature of the tumor because some sources have suggested that it may be the most immature form of an odontoma. This suggestion has recently been largely disregarded because further studies of odontogenic lesions indicated that the age

groups for the two lesions were identical, and the incidences and sex predilection of the two lesions differed, factors that should be the same if ameloblastic fibroma evolves into odontoma.

CLINICAL FEATURES

The ameloblastic fibroma most commonly occurs in young patients with an average age of 14 years. It has occasionally occurred in older patients up to the age of 40. It is slow growing and commonly located in the mandibular molar area, often over an unerupted tooth. If the ameloblastic fibroma is near the surface, slight buccal and lingual cortical expansion is evident. Other symptoms are frequently missing.

RADIOGRAPHIC FEATURES

Lesions are most often over an unerupted tooth. They are unilocular or multilocular radiolucencies (Figure 5-33) that are well corticated and vary considerably in size.

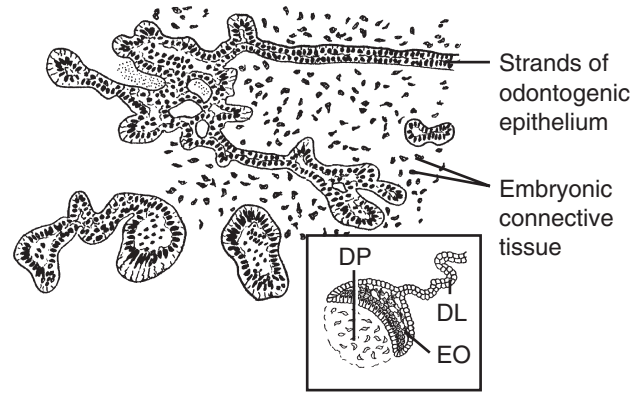
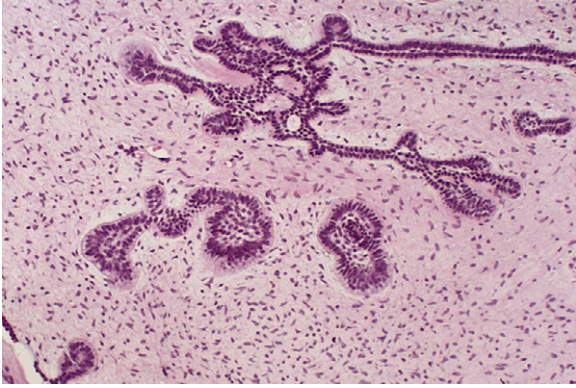
HISTOPATHOLOGY

The microscopic appearance consists of thin strands and cords of odontogenic epithelium that resembles the dental lamina and the cap and bell stages of early odontogenesis. The background is composed of embryonic connective tissue containing randomly oriented and widely separated fibroblasts (Figure 5-34). Zones of hyalinization, sometimes with associated focal areas of calcification, are often found surrounding the epithelial component of the lesion.



FIGURE 5-33

Ameloblastic fibroma. Panoramic radiograph of multilocular radiolucent lesion superior to the crown of an impacted mandibular first molar.

**FIGURE 5-34**

Ameloblastic fibroma. Microscopic features consist of strands and islands of odontogenic epithelium resembling the dental lamina and cap stage of odontogenesis. Tumor recapitulates the invagination of the dental lamina and cap stage of the earliest phases of odontogenesis (inset). DL, Dental lamina; DP, dental papilla; EO, enamel organ.

TREATMENT

The lesion is well encapsulated and easily separated from the surrounding bony crypt. There have been a relatively high number of recurrences for a benign lesion. As the lesion is well circumscribed, recurrences are considered to be the result of inadequate initial removal of what are frequently multilobular lesions.

ODONTOMA

ODONTOMA: *A usually hamartomatous lesion commonly found over unerupted teeth and containing enamel, dentin, pulp, and cementum in either recognizable tooth shapes (compound) or a solid, gnarled mass (complex).*

Odontomas are composed of mature enamel, dentin, and pulp and may be compound or complex, depending on the extent of morphodifferentiation or on their resemblance to normal teeth. Because most occur during the period of normal tooth development and often reach a fixed size, they are not considered true neoplasms, but hamartomas.

CLINICAL FEATURES

Odontomas are by far the most common noncystic odontogenic lesions, representing nearly 70% of all odontogenic tumors. Nearly all odontomas are found during the first and second decades. Odontomas more commonly occur in the maxilla than the mandible. Lesions are usually discovered when a tooth fails to erupt at its scheduled time (Figure 5-35, A). When the associated tooth is able to erupt around the odontoma, an asymptomatic swelling may be the only clinical evidence that a lesion is present.

ODONTOGENIC TUMORS

Predominantly Occurring in Young Patients

Odontoma
Cementoblastoma
Ameloblastic fibroma
Adenomatoid odontogenic tumor

RADIOGRAPHIC FEATURES

Compound odontomas are usually located in the anterior part of the mouth, either over the crowns of unerupted teeth or between the roots of erupted ones. Lesions are usually unilocular, containing multiple radiopaque structures that resemble miniature teeth (Figure 5-35, B). Compound odontomas may contain as few as 2 to 3 miniature toothlike structures or as many as 20 to 30 (Figure 5-36).

A **complex odontoma** is most commonly found in the posterior parts of the mandible over impacted teeth and can attain sizes up to several centimeters. They appear as a solid radiopaque mass exhibiting some nodularity and are surrounded by a thin, radiolucent zone (Figure 5-37). The lesions are unilocular and separated from normal bone by a distinct line of cortication. Individual toothlike structures are absent.

HISTOPATHOLOGY

The enamel, dentin, and pulpal tissue of the toothlike structures of compound odontoma are arranged in an orderly pattern. Within the surrounding capsule, a thin band of follicular connective tissue separates each miniature conical tooth. Complex odontoma differs by

**FIGURE 5-35**

Odontoma. **A**, Common clinical finding in patients with an odontoma is retention of a deciduous tooth and failure of the permanent tooth to erupt. **B**, Radiograph of same patient revealing the presence of multiple individual toothlike structures in a well-demarcated bone cavity impeding the eruption of the permanent central incisor.

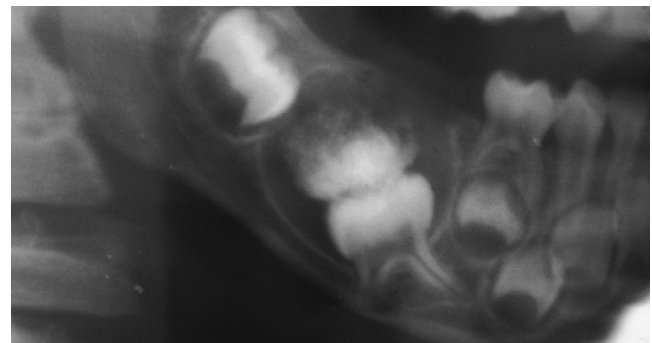
**FIGURE 5-36**

Compound odontoma. Multiple conical and irregularly shaped miniature teeth removed from within the capsule of a large lesion.

being composed of a single, gnarled, disorganized mass of enamel, dentin, and pulp, with no recognizable tooth shapes (Figure 5-38). Both compound and complex forms may also contain reduced enamel epithelium, secretory ameloblasts, and functional odontoblasts. Islands of odontogenic rests and spherical calcifications are common in the surrounding connective tissue.

TREATMENT

Both forms of odontoma are well encapsulated and easily enucleated from the surrounding bone. No recurrences have been recorded.

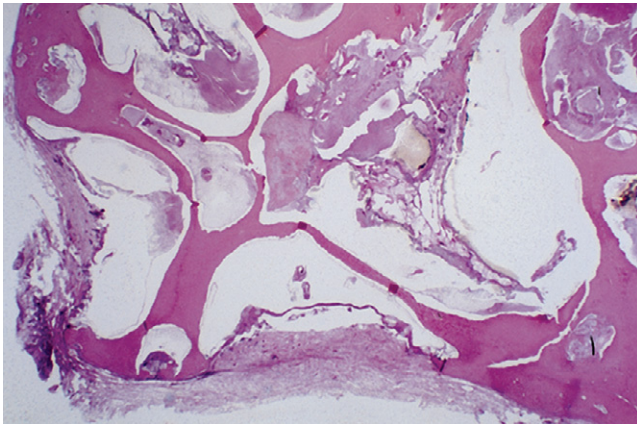
**FIGURE 5-37**

Complex odontoma. Radiograph of posterior mandible containing a dense structureless radiopacity preventing the eruption of an impacted molar in a young patient.

ODONTOGENIC TUMORS

Commonly Exhibiting Calcifications

- Adenomatoid odontogenic tumor
- Ameloblastic fibroma
- Cementoblastoma
- Odontoma
- Calcifying odontogenic cyst
- Ameloblastic fibro-odontoma
- Calcifying epithelial odontogenic tumor

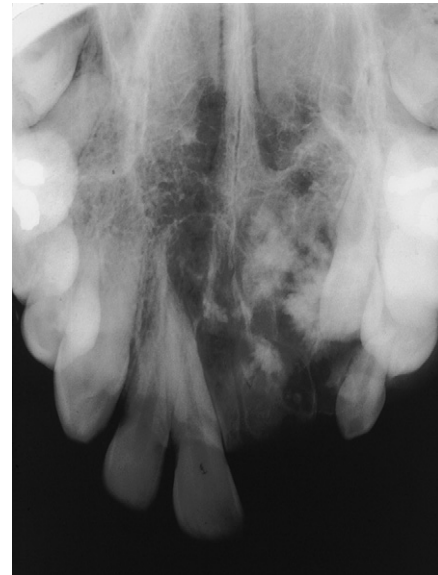
**FIGURE 5-38**

Complex odontoma. Microscopic appearance reveals irregular spaces containing residual elements of enamel matrix surrounded by septae of dentin interspersed with occasional areas of pulpal tissue. A fibrous connective tissue capsule is present in the periphery.

AMELOBLASTIC FIBRO-ODONTOMA

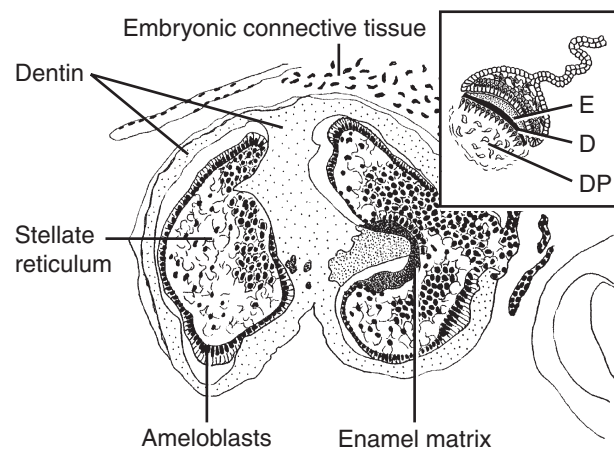
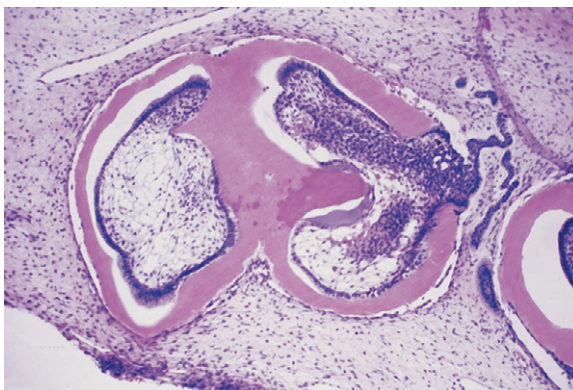
AMELOBLASTIC FIBRO-ODONTOMA: *An expansile growth in young patients that contains the soft tissue components of ameloblastic fibroma and the hard tissue components of complex odontoma.*

The ameloblastic fibro-odontoma is a recently defined entity in which both ameloblastic fibroma and

**FIGURE 5-39**

Ameloblastic fibro-odontoma. Radiograph of mixed radiolucent and radiopaque lesion of anterior maxilla preventing the eruption of the central incisor.

complex odontoma appear to be combined into one lesion. It has many clinical features in common with complex odontoma but differs significantly by having a greater potential for growth and local destruction. Care must be taken not to confuse this lesion with the **odontoameloblastoma**, an extremely rare form of ameloblastoma in which toothlike structures are included.

**FIGURE 5-40**

Ameloblastic fibro-odontoma. Photomicrograph of the irregularly shaped dentin deposits, enamel matrix, and odontogenic epithelium against a background of fibrillar connective tissue containing randomly oriented spindled cells. Tumor recapitulates cells from all phases of tooth development, including enamel and dentin production as found in the late bell stage of odontogenesis (*inset*). D, Dentin; DP, dental papilla; E, enamel.

CLINICAL FEATURES

The ameloblastic fibro-odontoma occurs in the first and second decades, the same age group as both odontoma and ameloblastic fibroma. It is primarily located in the posterior areas of the mandible but may be found in other locations. It appears as a slowly developing swelling of the affected portion of the jaw, usually in the area of an unerupted tooth. Pain is rarely associated with this lesion.

RADIOGRAPHIC FEATURES

The radiograph usually exhibits a large, unilocular, well-circumscribed, mixed radiolucent and radiopaque lesion. Multilocular lesions are occasionally encountered. The amount of soft and hard tissue components can vary extensively because both components are capable of dominating the lesion. The opacities are usually diffuse and nodular and present as a single large area or as several smaller dispersed deposits (Figure 5-39). Most lesions also contain an impacted tooth.

HISTOPATHOLOGY

The radiolucent areas are composed of soft tissue that resembles ameloblastic fibroma. These areas consist of strands and cords of epithelium that resemble dental lamina against a background of embryonic connective tissue composed of randomly oriented fibroblasts. In adjacent areas, both mature and immature forms of complex odontoma can be found (Figure 5-40). The lesion may be slightly lobular but is always surrounded by a well-formed capsule.

TREATMENT

Ameloblastic fibro-odontoma is treated in the same manner as ameloblastic fibroma. Careful enucleation is required because the possibility of recurrence exists if lesional tissue remains.

MALIGNANT ODONTOGENIC TUMORS

Because several of the odontogenic tumors can be locally destructive and even life threatening, particularly when located in the maxilla, the designation of malignancy in odontogenic tumors is best reserved for those in which documented metastasis has occurred. At times the designation is used to predict the anticipated future behavior of some odontogenic lesions that have cytologic features that are usually associated with malignancy. Even when using both of these criteria, the reported incidence of true malignant odontogenic tumors has been extremely low. The following is one classification of malignant epithelial odontogenic tumors. The lesions are presented in ascending order of degree of malignancy.

MALIGNANT AMELOBLASTOMA

MALIGNANT AMELOBLASTOMA: *A lesion with the histopathologic features of common ameloblastoma in which documented metastasis has occurred.*

A small number of ameloblastomas that appear cytologically benign have been documented in which a metastasis has occurred to regional lymph nodes or to other distant sites, the lungs being most common. In many cases these ameloblastomas recurred repeatedly, requiring multiple surgical procedures; in other cases the metastasis occurred when the lesion was first discovered. Thus presence of a documented metastasis in an otherwise cytologically benign-appearing ameloblastoma has been termed *malignant ameloblastoma*.

AMELOBLASTIC CARCINOMA

AMELOBLASTIC CARCINOMA: *An aggressive neoplasm of the mandible or maxilla in which the epithelial component exhibits features of ameloblastoma but with notable cytologic malignancy.*

The ameloblastic carcinoma differs from malignant ameloblastoma in that portions of its epithelial component are composed of cytologically malignant cells, yet the lesion is still readily recognizable as ameloblastoma (Figure 5-41). The histologic features portend the aggressive behavior of the lesion. If metastasis has not already occurred at the time of discovery, surgery (more aggressive than usual for ameloblastoma) is required to prevent this eventuality.

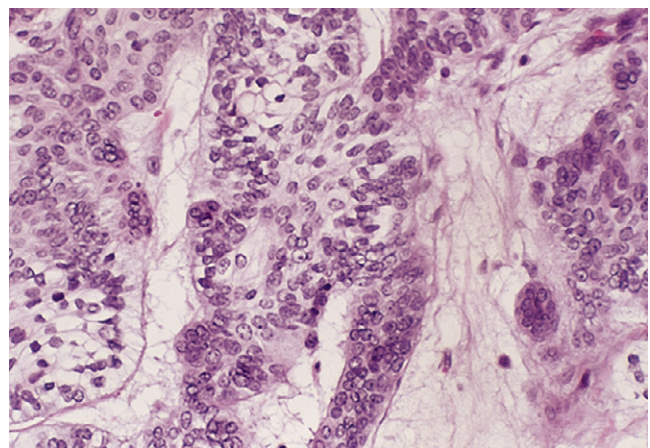
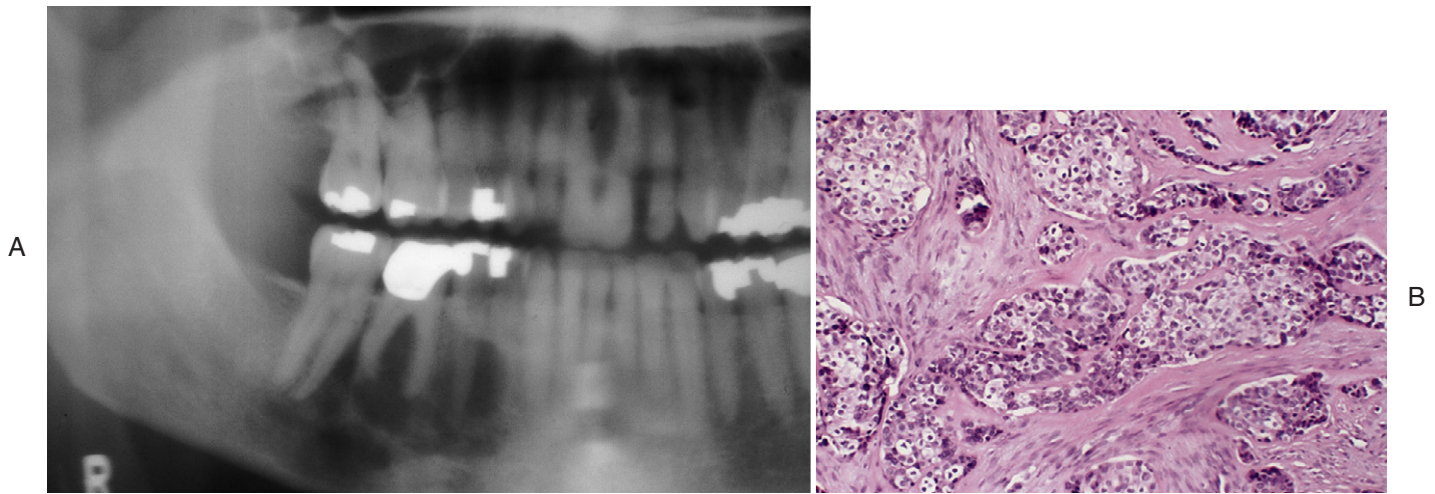


FIGURE 5-41

Ameloblastic carcinoma. Microscopic findings reveal features of ameloblastoma (*left bottom*) and cellular atypia of malignancy (*center and right*).

**FIGURE 5-42**

Odontogenic carcinoma. **A,** Panoramic radiograph exhibiting a diffuse, multilocular mottled radiolucency of posterior mandible. **B,** Microscopic features consist of islands and lobular accumulations of clear and eosinophilic epithelial cells exhibiting atypia and an infiltrative pattern.

ODONTOGENIC CARCINOMA

ODONTOGENIC CARCINOMA: *An aggressive and destructive intraosseous lesion of the mandible or maxilla that consists of poorly differentiated epithelial cells and clear cells in a pattern that is reminiscent of early odontogenesis.*

The odontogenic carcinoma is an uncommon intraosseous epithelial malignancy that has features that are indicative of an odontogenic origin but not specific enough to relate it to a particular benign odontogenic tumor. The radiographic appearance exhibits a diffuse “honeycomb” radiolucency, a feature that is consistent with an aggressive destructive intraosseous lesion (Figure 5-42, A). Most lesions have a significant portion of their neoplastic element composed of islands and strands of clear cells (Figure 5-42, B). The nonclear cell epithelial component resembles cells of the dental lamina. The epithelial structures are usually surrounded by zones of myxomatous connective tissue reminiscent of the inductive activity that occurs in odontogenesis. The usual features of malignancy, such as high mitotic index, hyperchromatism, and pleomorphism, are not usually found in these lesions. Their relative cytologically benign appearance often masks their sinister identity. Odontogenic carcinoma is difficult to cure because it is very infiltrative and has a high rate of recurrence.

PRIMARY INTRAOSSEOUS CARCINOMA

PRIMARY INTRAOSSEOUS CARCINOMA: *A squamous cell carcinoma within the mandible or maxilla with no indication that it originated from surface epithelium or that it metastasized from another site.*

When located within the jaws, particularly when no breach of the overlying mucosa exists, the lesion is considered a malignant neoplasm of odontogenic origin. This is because the remnants of odontogenesis are the only source of intraosseous epithelium once a metastasis from a distant site has been ruled out. In the maxilla, assuming an odontogenic origin is much more difficult, because epithelium is present in the lining of the sinuses and in nasopalatine duct cysts. The primary intraosseous carcinoma behaves like any other intraosseous malignancy, destroying large areas of bone (Figure 5-43, A), resorbing roots of teeth, invading nerve trunks, and metastasizing regionally and to distant organs. In many intraosseous carcinomas, evidence of their origination from the lining of a preexisting odontogenic cyst, most commonly a dentigerous cyst, can be found (Figure 5-43, B).

Treatment is the same as for any squamous cell carcinoma of the head and neck that has deeply infiltrated bone. It is usually aggressive and often requires neck dissection for removal of regional lymph nodes followed by radiation and, at times, chemotherapy.

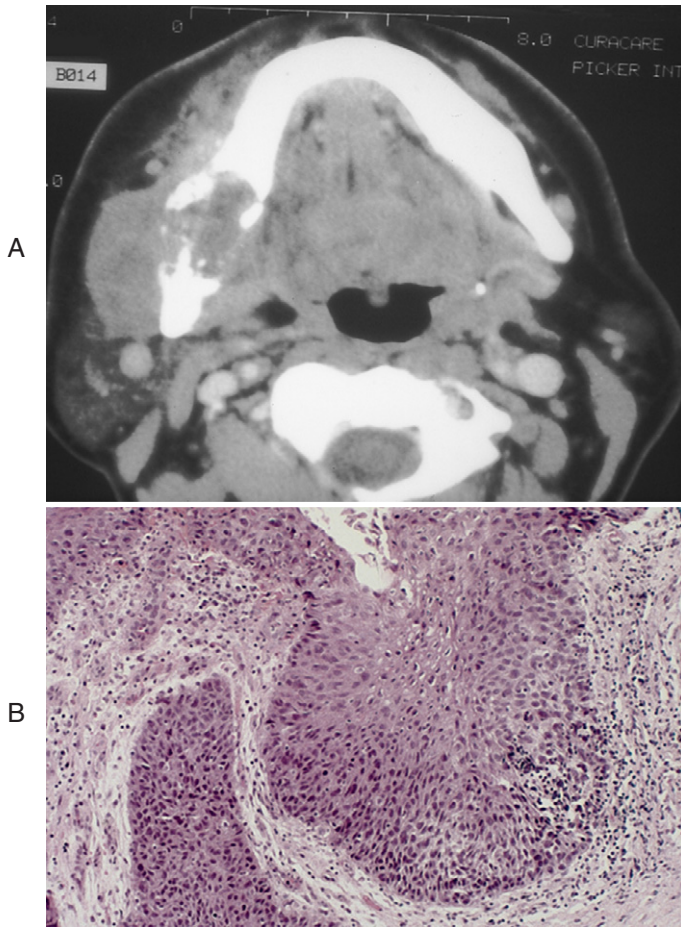


FIGURE 5-43

Primary intraosseous carcinoma. **A**, Computed tomography of posterior mandible demonstrating a large area of bony destruction. **B**, Photomicrograph of squamous cell carcinoma within body of mandible with features that indicate origination from the epithelial lining of a cyst.

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6 *Epithelial Disorders*

CHAPTER OUTLINE

BENIGN EPITHELIAL LESIONS

Squamous Papilloma
Keratoacanthoma

BENIGN PIGMENTED LESIONS

Melanotic Macules
Smoker's Melanosis
Nevi
 Intramucosal (Intradermal) Nevus
 Junctional Nevus
 Compound Nevus
 Blue Nevus
 Spitz Nevus
Seborrheic Keratosis
Actinic Lentigo
Peutz-Jeghers Syndrome
Melasma
Acanthosis Nigricans

LEUKOPLAKIA

EPITHELIAL HYPERPLASIA

Hyperkeratosis
Acanthosis
Nicotine Stomatitis
Proliferative Verrucous Leukoplakia

EPITHELIAL ATROPHY

Oral Submucous Fibrosis

EPITHELIAL DYSPLASIA

Carcinoma In Situ

ERYTHROPLAKIA

MALIGNANT EPITHELIAL NEOPLASMS

Squamous Cell Carcinoma
 Carcinogenic Factors
 Sites and Incidence
 Metastasis
 Less Common Forms of Squamous Cell Carcinoma

MELANOMA

Skin and Mucosal Melanoma
Superficial Spreading Melanoma
Lentigo Maligna Melanoma
Acral Lentiginous Melanoma
Nodular Melanoma

METASTASES TO THE JAWS

ADDITIONAL KEY TERMS

Actinic cheilitis
Epidermoid carcinoma
Hyperorthokeratosis
Hyperparakeratosis
Keratinizing carcinoma
Labial melanotic macule
Lichenoid dysplasia
Nonkeratinizing carcinoma
Oral melanoacanthomas
Oral melanotic macule
Orthokeratin
Parakeratin
Pseudoepitheliomatous hyperplasia
Smoker's keratosis
Speckled erythroplakia
Undifferentiated carcinoma
Verrucous hyperplasia



The oral cavity is lined by a membrane composed of stratified squamous epithelium. This epithelium serves as a cover for the oral soft tissues and as a barrier to the entry of external pathogenic factors. Depending on the intraoral site, the stratified squamous epithelium may be nonkeratinized, orthokeratinized, or parakeratinized. In addition, the thickness of the squamous epithelium differs from one anatomic site to the next. For example, the epithelium of the hard palate is normally thick and exhibits a surface layer composed of **orthokeratin**, whereas the epithelium of the soft palate is thin and nonkeratinized. A detailed knowledge of the normal microscopic features of the epithelium at the various intraoral sites is essential when tissue is microscopically evaluated for the presence of abnormalities.

An important component in diagnosing diseases of epithelium is an evaluation of the melanocytes. These melanin-producing cells are normally found between the cells of the basal cell layer of squamous epithelium where their numbers vary between different anatomic sites but not between individuals with different degrees of skin pigmentation. Differences in skin color appear to be related to differences in reactivity of melanocytes, not to the number of melanocytes. Whether oral pigmentation is clinically visible or not depends on the amount of melanin elaborated by the melanocytes. In light-skinned individuals, the oral mucosa normally exhibits a uniform salmon-pink coloration. Individuals who are dark-skinned will often exhibit some pigmentation of the oral mucous membranes. Such intraoral pigmentation has been termed *physiologic* or *racial pigmentation* and is usually most conspicuous on the labial gingiva but is also seen on the buccal and labial mucosa.

Multiple local and systemic factors can affect the oral epithelium and alter its normal clinical and microscopic features. Chronic local physical irritants such as tobacco smoke can stimulate the normally thin nonkeratinized squamous epithelium to become keratinized and thickened. In addition, constituents of tobacco smoke can stimulate the melanocytes to elaborate increased amounts of melanin that can result in both local and generalized pigmentation of the oral mucosa (**smoker's melanosis**).

Because numerous local and systemic factors affect the oral mucous membranes, a broad spectrum of hamartomatous, reactive, inflammatory, autoimmune, infectious, pigmented, dysplastic, and neoplastic lesions of epithelial origin are found in the oral cavity. These lesions may be local or diffuse and may appear clinically as macular, papular, papillary, white (leukoplakic), red (erythroplakic), ulcerated, pigmented lesions or as large ulcerated tumor masses. In this chapter the diseases that affect the epithelium are discussed un-

der the general headings of benign, hyperplastic, and malignant lesions.

BENIGN EPITHELIAL LESIONS

SQUAMOUS PAPILLOMA

SQUAMOUS PAPILLOMA: A benign exophytic papillary growth of stratified squamous epithelium.

Squamous papilloma, often termed *papilloma*, is a benign epithelial growth with a cause that has not yet been completely elucidated. It has been shown that human papilloma virus (HPV) causes many benign papillary growths of the oral mucosa. Because it is not always possible to detect a virus within the epithelial cells of these lesions, the possibility exists that a form of focal papillary epithelial proliferation is not caused by HPV but represents a true benign epithelial neoplasm. Some investigators contend that all forms of focal papillary epithelial hyperplasia have a viral etiology. Because these lesions exhibit a number of the morphologic features seen in verruca vulgaris and condyloma acuminatum, both of which are known to be caused by HPV, they still may have a viral cause but with viral counts below the detection threshold of current diagnostic laboratory methods. Until diagnostic probes are available to detect HPV in all benign papillary epithelial growths, lesions lacking evidence of HPV infection are considered to be squamous papillomas.

CLINICAL FEATURES

The squamous papilloma is an exophytic papillary lesion that usually measures less than 1 cm in greatest diameter. It may be sessile or pedunculated and white (keratinized) or pink (nonkeratinized). Most lesions are solitary and commonly occur on the soft palate, uvula, and ventral and dorsal surfaces of the tongue, gingiva, and buccal mucosa (Figure 6-1).

HISTOPATHOLOGY

A thick papillary layer of keratinized or nonkeratinized squamous epithelium and a central core of fibrovascular connective tissue characterize the squamous papilloma (Figure 6-2). The papillary projections may be long and fingerlike or short, rounded, and blunt. The epithelium generally exhibits a normal maturation pattern, although a mild degree of basilar hyperplasia is sometimes seen. The histologic variations seen in squamous papilloma may represent the normal morphologic spectrum of a single lesion, or it may be an indication that squamous papilloma is a heterogeneous group of papillary lesions with different causes. The latter possibility is likely, because three of the lesions, once lumped within the spectrum of squamous papilloma (oral ver-



FIGURE 6-1
Papilloma of the left ventral surface of the tongue.

ruca vulgaris, oral condyloma acuminatum, focal epithelial hyperplasia [Heck disease]), are now considered separate and distinct entities caused by different subtypes of HPV (see Chapter 7).

TREATMENT

The treatment of squamous papilloma consists of simple surgical excision of the base of the lesion and a small area of surrounding normal tissue. Recurrence is uncommon.

KERATOACANTHOMA

KERATOACANTHOMA: A benign endophytic epithelial growth appearing as a well-circumscribed keratin-filled crater on sun-exposed skin; often mistaken for squamous cell carcinoma.

The keratoacanthoma (KA) is a benign epithelial neoplasm that primarily occurs on sun-exposed skin, especially on the faces of patients 50 years of age and older. The male to female ratio for this tumor is approximately 2:1. Although most lesions occur on hair-bearing skin (cheeks, nose, eyelids, ears), they also occur on the lower lip. It is believed that the neoplasm

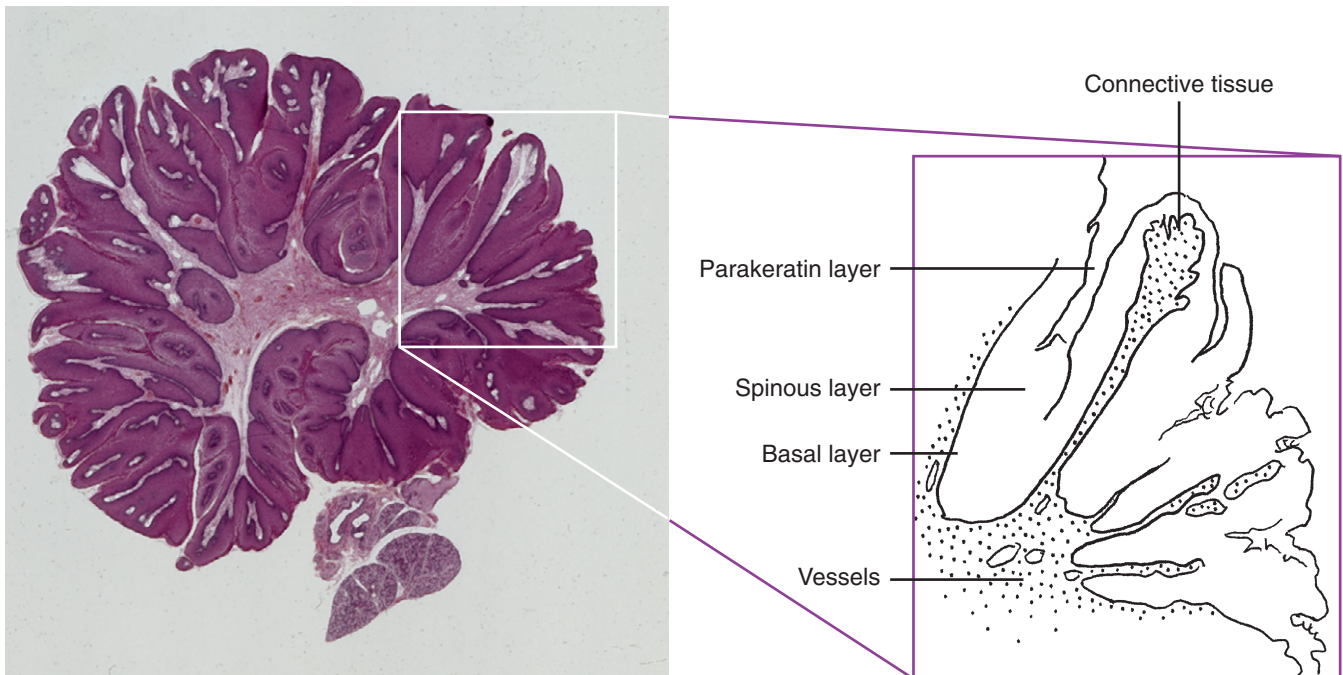


FIGURE 6-2
Papilloma. Low-power microscopic appearance with a diagrammatic inset illustrating the papillary projections composed of epithelium with thickened parakeratin and spinous cell layers and a central core of fibrous tissue with enlarged vascular structures.

arises from the hair follicle epithelium above the sebaceous glands. On the lower lip, it probably arises from the superficial epithelium of sebaceous ducts or from the hair follicle epithelium of adjacent skin.

CLINICAL FEATURES

Most KAs develop rapidly over a period of 1 to 2 months and occur as sharply circumscribed, bud-shaped nodules exhibiting a central keratin plug or keratin-filled crater (Figure 6-3). Its clinical appearance, rapid growth, and histologic appearance are all suggestive of squamous cell carcinoma. However, it frequently regresses spontaneously (without treatment), suggesting that it is benign.

HISTOPATHOLOGY

When viewed at low magnification, the microscopic appearance of KA resembles a well-differentiated squamous cell carcinoma. However, on closer observation, several



FIGURE 6-3
Keratoacanthoma of the lower lip. (Courtesy Dr. R.J. Achterberg.)

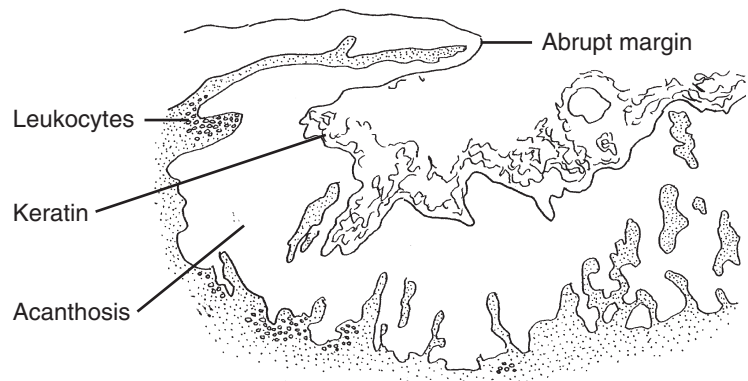
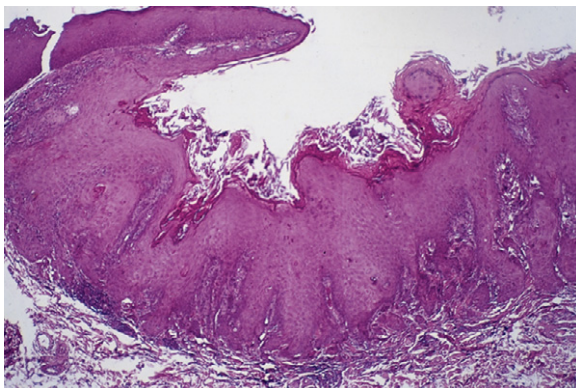


FIGURE 6-4
Keratoacanthoma. Distinguishable microscopic features of one edge of the lesion demonstrating the cup-shaped appearance with a depressed center containing a keratin plug and the pseudocarcinomatous growth pattern of the basal cell layer.

important distinguishing features reveal its benign nature. These include a central plug of keratin surrounded by a sharply demarcated, cup-shaped buttress of normal epidermis (Figure 6-4); epithelium exhibiting a pseudocarcinomatous rather than a true carcinomatous growth pattern; and epithelium composed of well-differentiated spinous cells with abundant cytoplasm and minimal nuclear pleomorphism, infrequent mitotic figures, and an absence of abnormal mitotic figures. The surrounding connective tissue usually exhibits a moderate to marked infiltrate of chronic inflammatory cells.

TREATMENT

Although KAs regress spontaneously if left untreated, in most cases the lesions are treated surgically before they reach their maximum size of 2.0 to 2.5 cm. Additionally, untreated lesions that regress on their own usually leave a depressed scar which may be cosmetically unacceptable. Surgical excision of the lesion is considered the treatment of choice, because this procedure is simultaneously curative, cosmetically acceptable, and provides a good tissue specimen to microscopically confirm the diagnosis.

BENIGN PIGMENTED LESIONS

A spectrum of pigmented lesions can occur within the oral cavity. The lesions described in this section are benign, and their pigmentation is largely caused by the excessive production of melanin. Melanin is produced by melanocytes, a specialized population of dendritic cells that normally reside in the basal cell region of squamous epithelium in skin and mucous membranes. Increases in the number of melanocytes or amount of melanin produced by these cells usually result in increased clinically visible pigmentation. Depending on the amount and

distribution of melanin present in the skin or mucosa, the color of a lesion will range between shades of brown, gray, black, and dark blue. Three explanations for the differences in the coloration of pigmented lesions are (1) lesions with melanin confined to the basal cells appear brown, (2) lesions with melanin in the keratin and in the spinous cells appear black, and (3) lesions with melanin in the deeper connective tissues appear blue.

MELANOTIC MACULES

MELANOTIC MACULES: *Physiologic or reactive small, flat, brown areas of the mucosal surfaces caused by an increase in the production of melanin granules but not an increase in the number of melanocytes.*

Small, pigmented macules occasionally occur on the lips and oral mucous membranes. The lip lesion is termed a **labial melanotic macule** and the intraoral lesion an **oral melanotic macule**. Although many melanotic macules of the mucosa represent foci of postinflammatory pigmentation, some may represent true ephelides (freckles).

CLINICAL FEATURES

The labial melanotic macule is an asymptomatic, small, flat, brown to brownish-black lesion that is primarily found on the vermilion border of the lower lip (Figure 6-5). Lesions can occur in patients at any age and are usually solitary but occasionally multiple. Most macules measure less than 5 mm in diameter and tend to occur near the midline of the lip.

An oral melanotic macule is the same lesion as the labial melanotic macule, except that it occurs within the confines of the oral cavity (Figure 6-6). Most oral melanotic macules are less than 1 cm in diameter and primarily occur on the gingiva, buccal mucosa, and soft palate.



FIGURE 6-5
Labial melanotic macule of lower lip.

On rare occasions, solitary or multiple lesions varying in color from dark brown to black and ranging in size from 5 mm to over 2 cm in diameter have occurred on the buccal mucosa and palate of 20- to 40-year-old African-American patients. These lesions are termed **oral melanoacanthomas**. The lesions are characterized by a proliferation of melanin-laden dendritic melanocytes; many present above the basal layer in an area of focally thickened epithelium. The epithelium exhibits marked acanthosis and a mild parakeratosis. Oral melanoacanthomas can develop within a few months and occasionally resolve without treatment.



FIGURE 6-6
Oral melanotic macule. Darkly pigmented area on the anterior maxillary alveolar ridge.

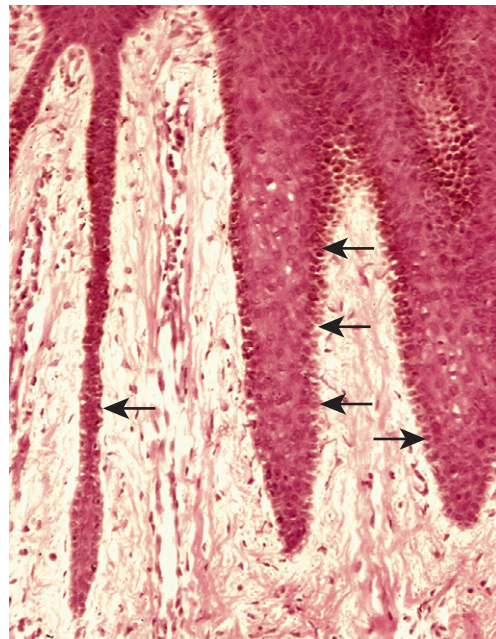


FIGURE 6-7
Melanotic macule. Microscopic features reveal an increase in the density of melanin granules in the basal cell layer (arrows).

HISTOPATHOLOGY

The histologic features of labial and oral melanotic macules are identical. They are characterized by an increase in melanin granules in the basal cell layer (Figure 6-7). The melanocytes are confined to the basal cell region and are usually within the normal numeric range. Occasionally, the melanocytes exhibit a conspicuous clear cytoplasm; however, nuclear atypia is absent. The basilar region of the epithelium and the superficial connective tissue often exhibit a mild infiltrate of lymphocytes and histiocytes. Small granular deposits of melanin, some within tissue histiocytes, are often visible in the superficial connective tissue. The dropout of melanin from the melanin-containing basal epithelial cells into the underlying connective tissue where it accumulates within macrophages is termed *melanin incontinence*.

TREATMENT

Although many melanotic macules arise slowly over time, some develop relatively quickly. Because a precise diagnosis may not be attainable through clinical examination alone, melanotic macules that arise within a short period should be excised to establish the actual diagnosis and to rule out the possibility of melanoma.

SMOKER'S MELANOSIS

SMOKER'S MELANOSIS: Irregular brownish macular pigmentation of the oral mucosa resulting from prolonged tobacco smoking.

Cigarette and pipe smoking commonly cause varying degrees of pigmentation of the oral mucosa. The increased pigmentation appears to be related to a constituent of tobacco smoke that stimulates increased melanin production. A mild degree of smoker's melanosis is common in both male and female smokers and may be difficult to detect clinically, especially in individuals who exhibit significant amounts of normal physiologic pigmentation. Because some female hormones are known to amplify melanin pigmentation, a more intense mucosal pigmentation may occur in female smokers who use contraceptive pills.

CLINICAL FEATURES

Smoker's melanosis is usually most conspicuous on the maxillary and mandibular anterior labial gingiva. Other intraoral sites commonly affected include the buccal mucosa, the floor of mouth, and the soft palate (Figure 6-8). It has been reported that smoker's melanosis of the soft palate should be viewed with concern, because it has sometimes occurred in association with smoking-related diseases such as emphysema and bronchogenic carcinoma.

HISTOPATHOLOGY

A biopsy from an area of smoker's melanosis exhibits histologic features similar to those found in a melanotic macule. Increased melanin deposits are found within basal epithelial cells, and the underlying connective tissue exhibits a mild infiltrate of lymphocytes and histiocytes (Figure 6-9). The presence of melanin granules in the phagocytic cells of the superficial connective tissue (melanin incontinence) is common.

TREATMENT

The most effective treatment for smoker's melanosis is to stop smoking. This will usually result in elimination of the pigmentation within a few months. If the pigmentation persists after a period of not smoking, a biopsy to assess the lesion is advisable.



FIGURE 6-8

Smoker's melanosis of the buccal mucosa in an older patient who has smoked for many years.

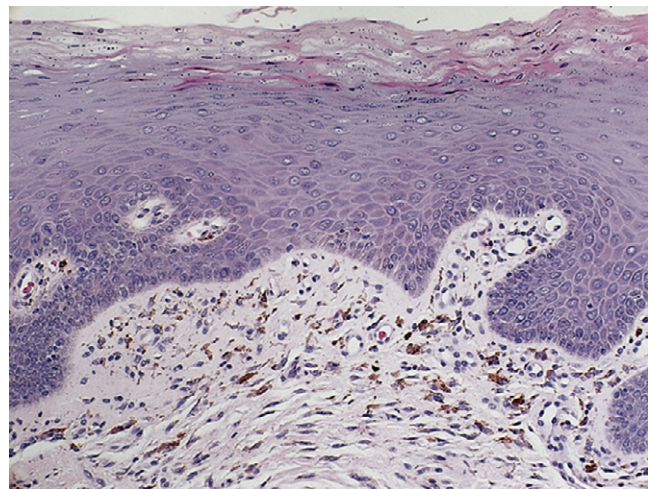


FIGURE 6-9

Smoker's melanosis. Microscopic features of melanin granules phagocytized by macrophages within the connective tissue in addition to the abundant granules present in the basal cells.

NEVI

NEVUS: A benign, exophytic, usually pigmented, congenital lesion of the skin or mucosa composed of focal collections (nests) of rounded melanocytes (nevi cells); specific lesions are classified as intradermal (mucosal), junctional, or compound; a macular form, usually of the hard palate, composed of fusiform cells, is termed blue nevus.

The term *nevus* has several meanings. The common lay term for nevus is *mole*. Most nevi occur on the skin; however, they occasionally occur on mucous membranes, including the oral cavity. Although intraoral nevi can occur in various sites, most are found on either the hard palate or the gingiva. Nevi are usually pigmented. Based on the distribution and morphology of nevus cells, nevi have been classified as intramucosal (intradermal), junctional, compound, and blue (Figure 6-10).

Intramucosal (Intradermal) Nevus

The terms *intramucosal nevus* and *intradermal nevus* are synonymous. The former occurs on mucosal surfaces, and the latter occurs on skin.

CLINICAL FEATURES

Intradermal nevus occurs in young patients and is one of the most common lesions of the skin, where it is commonly termed a *mole*. By comparison, the intramucosal nevus in the oral cavity is uncommon. The intramucosal

nevus of the oral cavity occurs as an asymptomatic, pigmented, brown to black, slightly elevated papule or flat macule on the hard palate or gingiva (Figure 6-11). The lesion grows very slowly and generally measures less than 1 cm in diameter. On the skin the lesion can be raised or flat and tan or dark brown. It will often contain more hair than the surrounding normal skin (Figure 6-12).

HISTOPATHOLOGY

The intramucosal nevus is characterized by nests (theques), cords or sheets of nevus cells confined to the connective tissue (Figure 6-13). The morphology of the cells in the intramucosal nevus is variable and includes epithelioid, lymphocyte-like, spindle, and multinucleated types. The amount and distribution of melanin is variable; some lesions have scant amounts. Mitotic figures are usually absent. A feature of the intramucosal nevus is the presence of a fibrous connective tissue zone, free of nevus cells, that separates the nevus cell theques from the overlying epithelium.

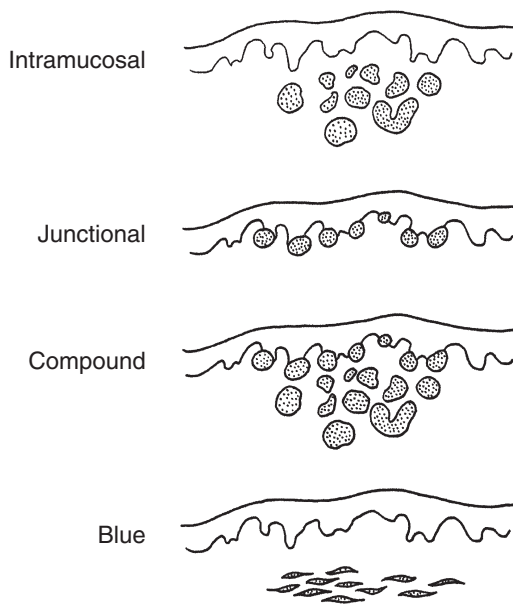


FIGURE 6-10

Four histologic types of intraoral nevi based on the location and shape of the nevus cells relative to the epithelium and the connective tissue.



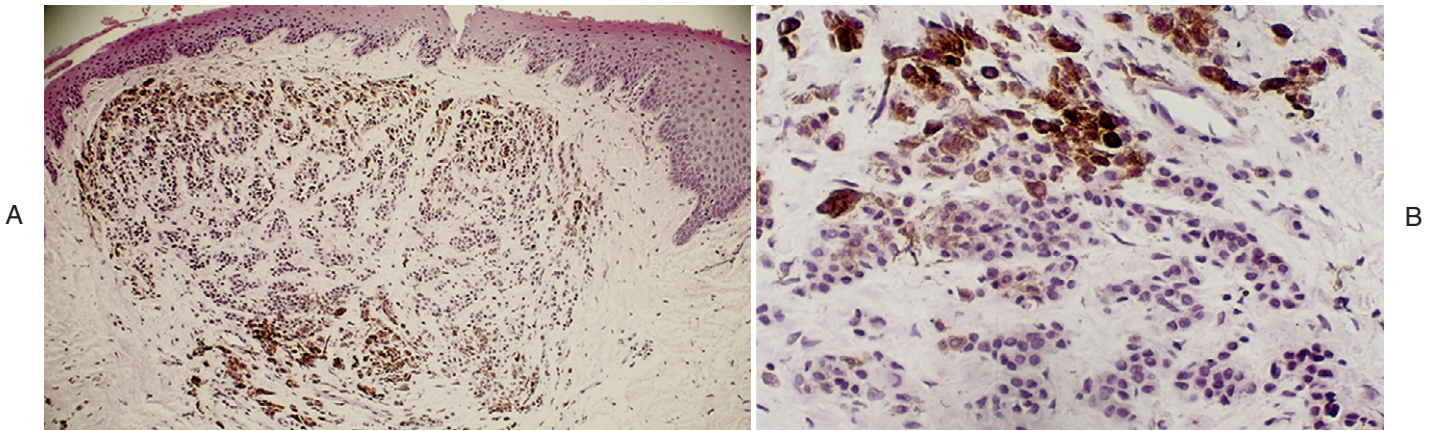
FIGURE 6-11

Intramucosal nevus presenting as a pigmented lesion of the palate.



FIGURE 6-12

Lightly pigmented intradermal nevus of the skin of the forehead.

**FIGURE 6-13**

Intramucosal nevus. **A**, Low-power microscopic appearance of the nevus cells confined to a circumscribed area and separated from the epithelium by a band of fibrous tissue. **B**, Higher magnification exhibiting the rounded or epithelioid form of the nevus cells arranged in characteristic clusters or nests (theques) with sporadic melanin production.

TREATMENT

As a general rule all solitary pigmented papules or nodules of the oral cavity should be excised and submitted for histopathologic evaluation. Intramucosal nevi are included in this category. Once excised, intramucosal nevi do not tend to recur.

Junctional Nevus

CLINICAL FEATURES

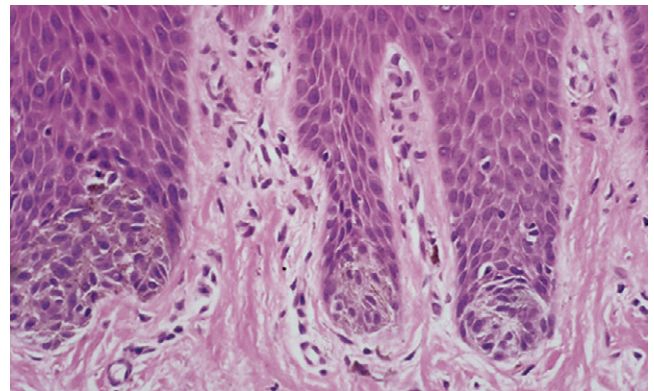
The junctional nevus is a benign, brown to black lesion that occurs primarily on the skin and occasionally on the oral mucosa. This type of nevus is considerably less common than the intramucosal (intradermal) nevus. Within the oral cavity it usually appears as a pigmented macular lesion on the hard palate or gingiva.

HISTOPATHOLOGY

The junctional nevus is characterized by the presence of nevus cell nests in the basilar region of the epithelium, primarily at the tips of the epithelial rete pegs. No nevus cells are found in the adjacent connective tissue (Figure 6-14). Careful examination of the individual cells is extremely important in the junctional nevus, because a similar type of focal proliferation of melanocytes (junctional activity) occurs in the early phases of *melanoma*—a malignant neoplasm composed of atypical melanocytes. It is important to note that a junctional nevus can occasionally undergo malignant transformation to a melanoma.

TREATMENT

For the previously mentioned reasons, a solitary pigmented lesion of the oral mucosa, particularly on the hard palate, should be excised and submitted for

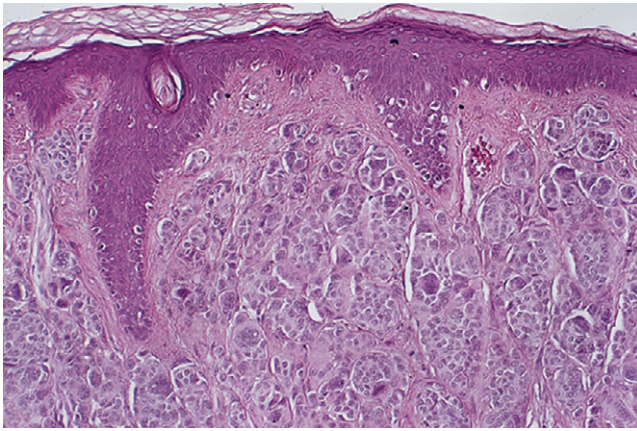
**FIGURE 6-14**

Junctional nevus. Microscopic appearance demonstrating the clusters of nevus cells confined to the basal cell layer of the epithelium.

histopathologic examination. Once excised, a junctional nevus does not tend to recur.

Compound Nevus

The compound nevus has the combined characteristics of the intramucosal nevus and the junctional nevus, exhibiting nevus cells in the basal region of the epithelium and in the adjacent connective tissue (Figure 6-15). As is true of the other nevi, the compound nevus is far more common on the skin than it is on the oral mucosa. Within the oral cavity it also tends to occur as a pigmented papule or macule on the hard palate or gingiva. As with other solitary pigmented oral lesions, the compound nevus is treated by an excisional biopsy that simultaneously serves as a diagnostic and therapeutic procedure.

**FIGURE 6-15**

Compound nevus. Microscopic appearance exhibiting features of the intramucosal and junctional nevus.

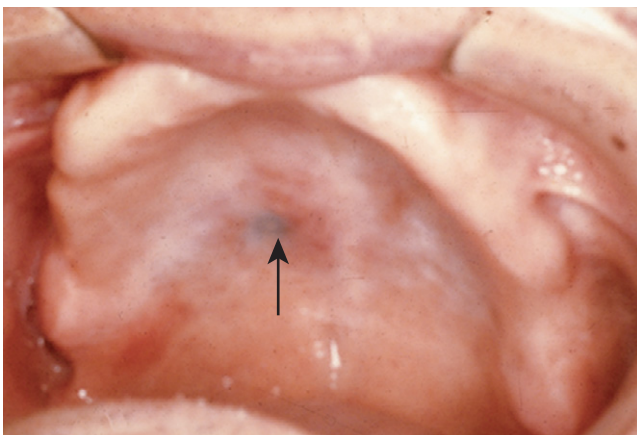
Blue Nevus

CLINICAL FEATURES

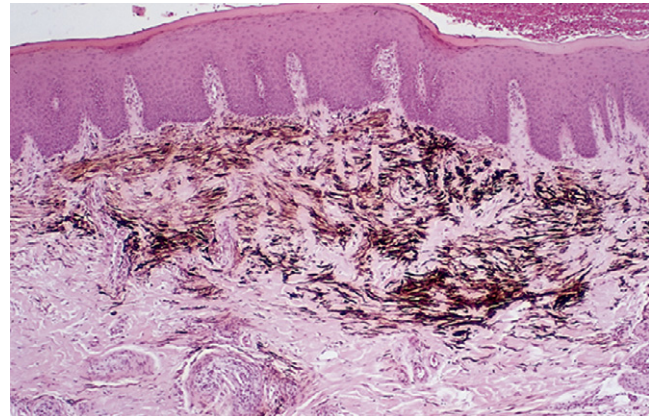
The blue nevus is a benign pigmented lesion that presents as a dark blue dome-shaped papule or as a flat macule on the skin or mucosa. Within the oral cavity the blue nevus occurs most commonly on the hard palate (Figure 6-16).

HISTOPATHOLOGY

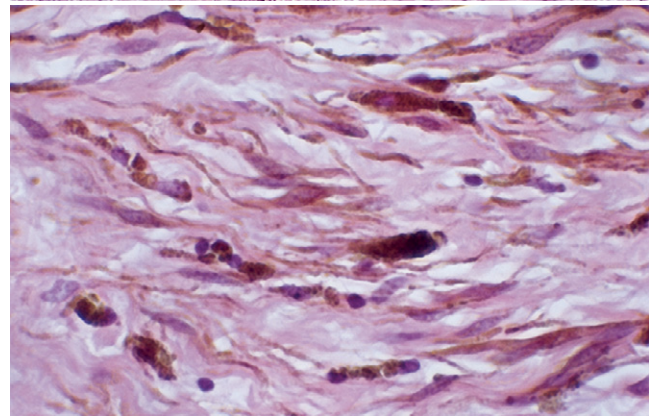
The melanin-producing cells of a blue nevus differ from those of the nevi previously discussed. In the blue nevus the pigment-producing cells are spindled and fusiform dendritic cells rather than rounded or epithelioid. The spindled dendritic nevus cells are confined to the connective tissue (Figure 6-17, A). Instead of being arranged in rounded clusters (theques), they tend to be separated

**FIGURE 6-16**

Blue nevus. The bluish lesion (arrow) is located in the middle of the hard palate, its most common intraoral location.



A



B

FIGURE 6-17

Blue nevus. **A**, Low-power microscopy illustrating the presence of melanin-laden cells confined to the connective tissue. **B**, High-power microscopy of lesion demonstrating the separated elongated spindle-shaped cells in their typical orientation parallel to the surface epithelium.

and parallel to the normal overlying epithelium (Figure 6-17, B). Variable numbers of melanin-containing macrophages (melanophages) are often present among the dendritic nevus cells. The blue nevus has no tendency to undergo malignant transformation.

TREATMENT

Because a blue nevus can clinically resemble a melanoma, a diagnostic excisional biopsy is usually performed, which also serves as the definitive treatment for this lesion.

Spitz Nevus

CLINICAL FEATURES

The Spitz nevus is also known as *spindle and epithelioid cell nevus* and formerly called a “benign juvenile melanoma.” It is an uncommon type of melanocytic nevus that typically presents as a solitary small pink to reddish-brown papule primarily on the skin of the face and extremities of children. The majority of these lesions occur on the skin and only rarely on the oral mucosa.

HISTOPATHOLOGY

The Spitz nevus is usually composed of a mixture of spindle-shaped nevus cells and large epithelioid nevus cells with abundant cytoplasm arranged in relatively well-circumscribed nests located at or near the dermal and epidermal interface. In this respect, it shares characteristics with the compound nevus. The epithelioid nevus cells may be multinucleated and may appear atypical. Mitotic figures can be seen near the superficial aspect of the lesion; however, atypical mitoses are not seen. Differentiating a Spitz nevus from a nodular melanoma can be difficult based on cellular morphology alone. The small size (5 to 6 mm in diameter), the symmetry of the lesion, and the young age of most of the patients are important considerations when dealing with the Spitz nevus.

TREATMENT

Because the Spitz nevus is a small benign lesion, conservative excision of the entire lesion is curative.

SEBORRHEIC KERATOSIS

CLINICAL FEATURES

Seborrheic keratosis is a common, benign, acquired skin lesion that occurs on the sun-exposed skin of the face and trunk of middle-aged and older adults. The lesions are often multiple, vary in size between 5 to 10 mm and usually present as well-circumscribed brownish papules that have a “stuck on” appearance. Many of the lesions exhibit a friable verrucous surface. Seborrheic keratosis is not considered to be a premalignant lesion.

HISTOPATHOLOGY

Seborrheic keratoses exhibit a variety of microscopic appearances. All types are characterized by a largely exophytic proliferation of benign basaloid keratinocytes with hyperkeratosis, acanthosis, and papillomatosis. Multiple keratin plugs and variable-sized concentric keratin islands are common features.

TREATMENT

Because seborrheic keratoses are insidious, often multiple, and enlarge slowly, they are commonly left untreated. The larger lesions are usually excised for cosmetic reasons. Simple curettage or cryosurgery with liquid nitrogen is often used to remove smaller lesions.

ACTINIC LENTIGO

CLINICAL FEATURES

Actinic lentigo, also termed *solar lentigo*, *senile lentigo*, *age spot*, or *liver spot*, is a benign pigmented macular lesion that usually presents as multiple lesions on sun-exposed skin, primarily on the face, exterior surfaces of the fore-

arms, and most commonly on the dorsal surfaces of the hands. Exposure to sunlight is the eliciting factor. These lesions are uncommon before the fifth decade of life, but are seen in more than 90% of Caucasian men and women who are 70 years of age or older. The lesions exhibit a uniform dark brown color and have an irregular outline. The lesions vary in diameter from minute to more than one centimeter. Actinic lentigo is a benign lesion that does not undergo malignant transformation.

HISTOPATHOLOGY

Slightly bulbous and marked elongated rete ridges with a marked increase in melanin content within the basal keratinocytes characterize the lesion. The number of melanocytes in these lesions may be normal or somewhat increased; however, nesting of melanocytes or junctional activity does not occur. Melanin incontinence and mild chronic inflammation may be seen in the upper dermis.

TREATMENT

No treatment of actinic lentigo is required. Treatment for esthetic reasons with topical retinoic acid can reduce the color intensity of the lesions. Laser treatment has also been used.

PEUTZ-JEGHERS SYNDROME

CLINICAL FEATURES

Peutz-Jeghers syndrome is an uncommon autosomal dominant disorder characterized by multiple intestinal polyps (intestinal polyposis) and by frecklelike pigmentation of the skin in periorificial areas (perioral, periocular, perinostril, perianal). The skin of the fingers, genital region, and oral mucosa can also be affected. The pigmented skin lesions become apparent in early childhood as small, brown to blue-gray macules that measure 1 to 4 mm in diameter. The gastrointestinal polyps seen in this syndrome primarily involve the ileum and jejunum and usually become apparent in the third decade of life. The intestinal polyps are capable of causing intussusception (telescoping of the bowel) that can lead to ischemic bowel damage. In addition, 2% to 3% of affected patients develop intestinal adenocarcinoma. Recognition of the clinical characteristic of the oral and skin lesions can lead to early diagnosis of the disorder and evaluation of the gastrointestinal system.

MELASMA

CLINICAL FEATURES

Melasma, also known as the *mask of pregnancy*, is a symmetrical hyperpigmentation of the sun-exposed skin of the face and neck. The exact cause of this condition is unknown; however, it is strongly associated with pregnancy and the use of oral contraceptives that contain

estrogen and progesterone. The degree of pigmentation is variable and is more likely to be seen in females with dark complexions. The degree of pigmentation intensifies with increased exposure to sunlight.

HISTOPATHOLOGY

The epithelium exhibits an increase in melanin within basal keratinocytes. The superficial connective tissue may also display melanin within the phagocytes (melanin incontinence).

TREATMENT

Topical treatment with 3% hydroquinone and tretinoin is generally effective. The pigmentation can spontaneously resolve after parturition or after cessation of oral contraceptives.

ACANTHOSIS NIGRICANS

CLINICAL FEATURES

Acanthosis nigricans is an acquired dermatologic condition that primarily affects the areas of skin where large skin creases are normally present (e.g., axillae, neck, groin and genital region, submammary region). The oral mucosa and vulva can also be affected. The skin lesions are characterized by a hyperkeratinized, hyperpigmented papillomatous and corrugated area of brown skin. Acanthosis nigricans can be divided into benign and malignant types. The benign type can be inherited and can be clinically apparent in childhood. It can also be a sign of an existing pituitary tumor or other endocrine conditions. The malignant type of acanthosis nigricans usually occurs after 40 years of age and is a sign of an existing internal malignancy, most commonly a gastric carcinoma.

HISTOPATHOLOGY

Histologic examination reveals hyperkeratosis, papillomatosis, and mild acanthosis. Hyperpigmentation is usually minimal, inconspicuous, or absent. Because the histopathologic features of the benign and the malignant types of acanthosis nigricans are essentially the same, clinical correlation between the histopathologic diagnosis, the age of onset, and the rate of progression of the lesions needs to be considered. If the lesions appeared after the age of 40 years and are obviously increasing in size, then the patient should undergo a complete clinical examination to rule out the existence of an internal malignancy.

LEUKOPLAKIA

LEUKOPLAKIA: Clinical term used to denote mucosal conditions that produce a whiter than normal coloration of the mucous membranes.

The term *leukoplakia* literally means *white patch*. It is used as a clinical term only to describe a variety of white mucosal lesions. Some diagnosticians prefer to restrict this term to those lesions that cannot be easily removed by gently rubbing the superficial mucosa, thus excluding lesions that produce a pseudomembrane (slough). In 1978 the World Health Organization (WHO) further modified the concept by defining leukoplakia as “a white patch on the oral mucosa that can neither be scraped off nor classified as any other diagnosable disease.” In various parts of the world and among various diagnosticians, the use of the term may vary.

CLINICAL FEATURES

Leukoplakic lesions have an occurrence rate of 1.5% to 12%, depending on the specific population studied. In general, approximately 5.4% of the lesions will eventually in squamous cell carcinoma. If the patient is a smoker, this incidence can increase to as high as 16%. Lesions can vary from flat, smooth, and slightly translucent macular areas to thick, firm, rough-surfaced, and fissured, raised plaques. The most common intraoral sites for leukoplakia are the buccal mucosa (Figure 6-18), the floor of the mouth, the labial commissures, the lateral borders of the tongue, and the mandibular and maxillary alveolar ridges.

Although leukoplakic lesions occasionally occur in nonsmokers, the use of smoked and smokeless tobacco is considered a strong causative factor in their development. Other factors that are known to play a causative role in some leukoplakias include premalignant epithelial changes, Epstein-Barr virus (EBV) infection in patients with human immunodeficiency virus (HIV), chronic irritation caused by ill-fitting dentures, chronic infection by *Candida albicans*, chronic lichen planus, and some genetic disorders (Box 6-1).



FIGURE 6-18

Leukoplakia. Clinical white patch of unknown origin on the buccal mucosa.

BOX 6-1**Common Mucosal Conditions Presenting as Leukoplakia****REACTIVE**

Hyperkeratosis (Ortho-, Para-)
 Acanthosis
 Actinic cheilitis
 Snuff dipper's keratosis
 Nicotine stomatitis
 Heat/chemical burns

NEOPLASTIC

Epithelial dysplasia
 Carcinoma in situ (CIS)
 Squamous cell carcinoma
 Verrucous carcinoma

INFECTIONS

Chronic hyperplastic candidiasis
 Hairy leukoplakia
 Syphilitic mucous patch

IMMUNE MEDIATED

Lichen planus
 Lupus erythematosus

HEREDITARY

Leukoedema
 White sponge nevus

IDIOPATHIC

Hairy tongue
 Geographic tongue

HISTOPATHOLOGY

Because the term *leukoplakia* describes the clinical appearance of a lesion and not the exact nature of the tissue changes, a microscopic evaluation of the nature and the degree of the alterations that are present within the mucosal epithelium must be undertaken. The epithelial alterations range from normal physiologic reactions to benign, premalignant, and malignant changes. The most common epithelial alterations are an increase in the thickness of the keratin layer (hyperorthokeratosis, hyperparakeratosis) and an increase in the thickness of the spinous layer (acanthosis). Hyperorthokeratosis is the most consistent microscopic finding in a leukoplakic lesion and occurs in many benign, premalignant, and malignant epithelial lesions.

A number of tissue alterations contribute to the white appearance of epithelium. Because stratified squamous epithelium is an avascular tissue, its constituents (keratin and keratinocytes in oral mucosa) tend to be

white. The presence of a thickened layer of keratin or keratinocytes in hyperorthokeratosis, hyperparakeratosis, or acanthosis acts as an added optical barrier that obscures the red coloration of the blood vessels in the underlying connective tissue, imparting a white coloration to the mucosa. The development of a malignant proliferation of one or more of the epithelial layers also results in a similar clinical appearance. Changes in the underlying connective tissue can also impart a whitish appearance to the oral mucosa. This is usually the result of a decrease in the vascularity and an increase in the collagen content of the underlying connective tissue, such as occurs in fibrous scar formation and in areas of focal fibrous hyperplasia (traumatic fibroma).

DIAGNOSIS

Because clinical leukoplakic lesions can represent a diagnostic spectrum ranging from an inflammatory reaction to benign or malignant changes, determining the appropriate treatment for a particular lesion is an important clinical decision. The most reliable way to reach this decision is to obtain one or more biopsies of the lesion and to request a histopathologic evaluation by a qualified pathologist who has experience with lesions of this anatomic area.

BIOPSY: *The removal of a sample of living tissue for laboratory examination.*

A biopsy of a leukoplakic lesion is necessary to understand more clearly the nature of the disease process. This is accomplished by evaluating the histopathologic changes in the tissue. If the lesion is small, the entire lesion is removed and submitted for microscopic examination, which is termed an *excisional biopsy*. If the lesion is large, a small portion of the lesion is removed and submitted for microscopic examination, which is termed an *incisional biopsy*. When performing an incisional biopsy of a large lesion, it is important to exercise good judgment and obtain a sample that is most likely to lead to an accurate diagnosis. If the lesion is multifocal, it is generally prudent to obtain more than one biopsy specimen for laboratory examination.

TREATMENT

The treatment of a leukoplakia is based on the exact nature of the lesion, which is determined by histopathologic evaluation of the tissue. If the lesion is benign (not premalignant or malignant), in most cases attempts are made to remove possible local predisposing factors that may be causing the lesion. If the lesion exhibits premalignant changes such as moderate to severe dysplasia or is frankly malignant, appropriate steps must be taken to completely remove it.

EPITHELIAL HYPERPLASIA HYPERKERATOSIS

HYPERKERATOSIS: Excessively thickened layer of the stratum corneum composed of orthokeratin (hyperorthokeratosis) or parakeratin (hyperparakeratosis).

Hyperkeratosis is commonly used to denote any excessive thickening of the stratum corneum. Because the superficial layer of oral epithelium can be composed of either orthokeratin or parakeratin, excessive amounts are more precisely termed **hyperorthokeratosis** and **hyperparakeratosis**. On histopathologic examination the majority of leukoplakias are found to be hyperorthokeratosis (Figure 6-19, A) or hyperparakeratosis (Figure 6-19, B).

Depending on the specific intraoral site, normal mucosal epithelium is nonkeratinized, orthokeratinized, or parakeratinized (Table 6-1). Orthokeratin is nonnucleated keratin, whereas parakeratin exhibits shrunken (pyknotic) residual nuclei. Keratin functions as a protective barrier on normal skin or mucosa. Various stimuli, such as chronic frictional irritation caused by an ill-fitting denture, smoking, or the use of smokeless (chewing) tobacco, will usually induce keratinization of nonkeratinized epithelium and additional keratin formation in keratinized epithelium. The term *smoker's keratosis* is sometimes used to refer to a hyperkeratosis (hyperorthokeratosis or hyperparakeratosis) induced by cigarette, cigar, or pipe smoking. In many cases the hyperkeratosis is characterized by a uniform thickening of the keratin layer. In other cases, particularly on the labial mucosa, smoker's keratosis clinically appears as a series of slightly elevated delicate white striations. Histologic sections of the

Table 6-1 Characteristics of Normal Epithelium in Various Intraoral Sites

Epithelial Type	Thickness	Site
Orthokeratinized	Thick	Hard palate
		Gingiva
		Alveolar mucosa
Parakeratinized	Thick	Dorsal tongue
		Gingiva
		Alveolar mucosa
Nonkeratinized	Thick	Dorsal tongue
		Buccal mucosa
		Buccal vestibule
Nonkeratinized	Thin	Labial mucosa
		Labial vestibule
		Floor of mouth
		Ventral tongue
		Lateral tongue
		Soft palate
		Gingival sulcus

striated tissue exhibit a characteristic chevron or church-spire organization of the parakeratin (Figure 6-20).

Also depending on the specific intraoral site, normal mucosal epithelium is either thick or thin (see Table 6-1). Normally, thin oral epithelium is nonkeratinized. Nonkeratinized thin epithelium is particularly vulnerable to the development of premalignancy

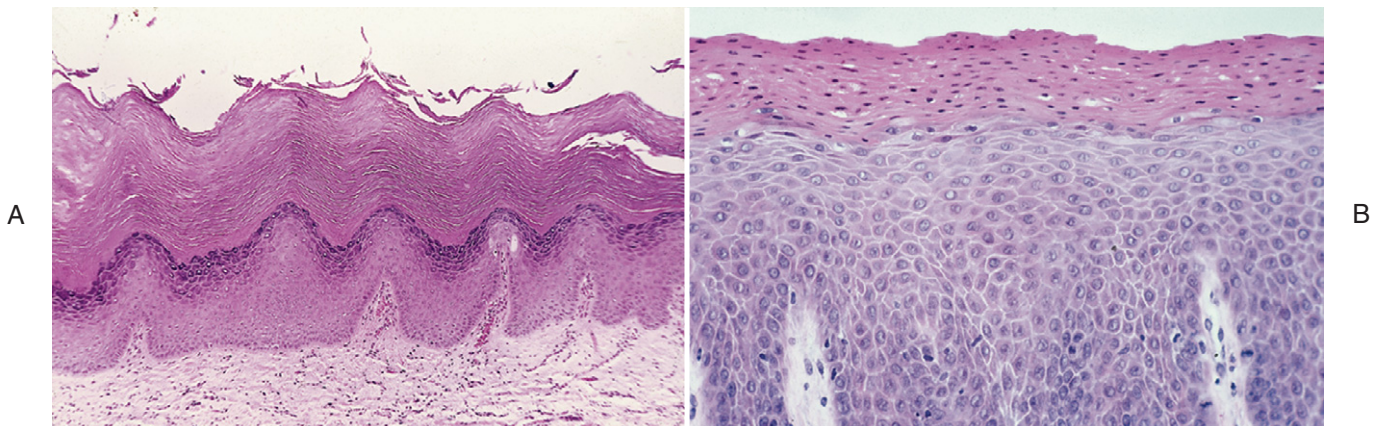
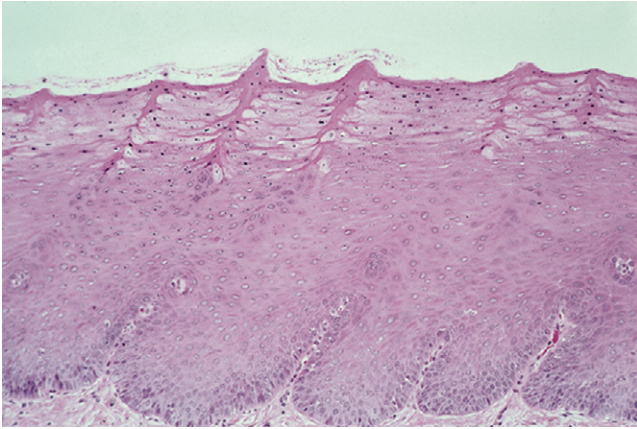


FIGURE 6-19

A, Hyperorthokeratosis. The keratin layer is without residual nuclei and is greatly thickened with an uneven surface. **B, Hyperparakeratosis.** The thickened keratin layer contains residual nuclei.

**FIGURE 6-20**

Smoker's keratosis. A unique tobacco-associated leukoplakia sometimes occurs on the labial mucosa, consisting of an increase in the orthokeratin or parakeratin layer and containing "chevron" or "church-spire" formations.

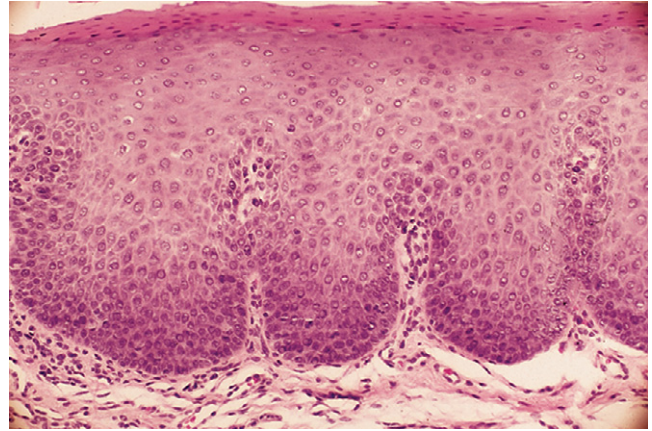
(epithelial dysplasia, carcinoma in situ [CIS] and malignancy (squamous cell carcinoma). For this reason, most intraoral squamous cell carcinomas in smokers occur at sites where the epithelium is thin and nonkeratinized (lateral borders of the tongue, floor of the mouth, ventral surface of the tongue, soft palate, gingival sulcus). In contrast, intraoral sites that are normally covered by keratinized thick epithelium (hard palate, dorsum of the tongue) are highly resistant to the development of squamous cell carcinoma.

ACANTHOSIS

ACANTHOSIS: Excessive thickening of the spinous layer of squamous epithelium, resulting in broadening and elongation of the rete pegs.

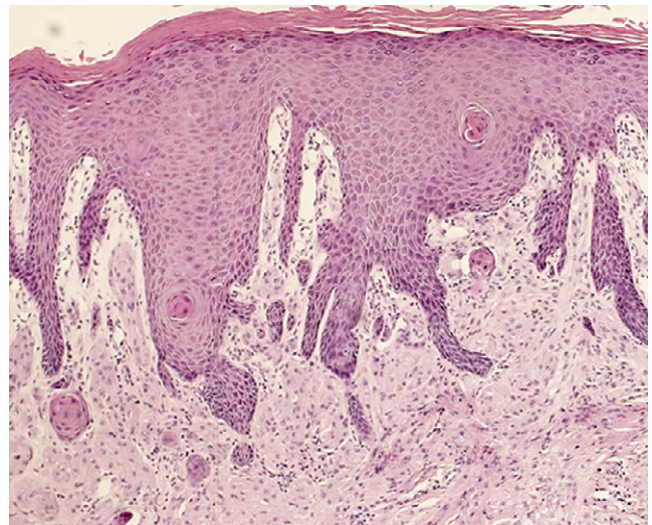
PSEUDOEPITHELIOMATOUS HYPERPLASIA: An excessive but benign proliferation of squamous epithelium that histologically resembles the proliferation seen in a squamous cell carcinoma.

Acanthosis is a benign hyperplasia of squamous epithelium characterized by an increase in the thickness of the spinous cell layer (Figure 6-21). Acanthosis may occur alone or, more commonly, in association with hyperkeratosis. In either case the thickened squamous epithelium obscures the coloration of the underlying blood vessels and is clinically seen as an area of leukoplakia. Like hyperkeratosis, acanthosis usually develops in response to chronic irritants, such as ill-fitting dentures, smoking or chewing tobacco, and infections such as chronic candidiasis. In most cases the architectural pattern of the acanthosis conforms to that of normal

**FIGURE 6-21**

Acanthosis. The intermediate cell layer of stratified squamous epithelium is extensively hyperplastic, resulting in both elongated and broadened rete pegs.

epithelium. Under certain conditions, however, acanthosis can cause the rete pegs to assume an irregular and exaggerated downward growth pattern that resembles squamous cell carcinoma. This type of acanthosis is termed *pseudoepitheliomatous hyperplasia (PEH)* (Figure 6-22). Oral conditions in which pseudoepitheliomatous hyperplasia is commonly seen include inflammatory papillary hyperplasia (palatal papillomatosis), chronic hyperplastic candidiasis, granular cell tumor, and blastomycosis.

**FIGURE 6-22**

Pseudoepitheliomatous hyperplasia. The epithelium is acanthotic, and the rete pegs are elongated in an irregular pattern that falsely (pseudo-) resembles squamous cell carcinoma.

NICOTINE STOMATITIS

NICOTINE STOMATITIS: A diffuse white change of the palate, the buccal mucosa, or both caused by a combination of hyperkeratosis and acanthosis, frequently exhibiting multiple small dimpled nodules around minor salivary duct openings; found primarily in chronic pipe smokers.

Nicotine stomatitis is a term used to describe a specific type of epithelial hyperplasia that primarily involves the hard palate of long-term pipe smokers. It is also occasionally seen in cigar or cigarette smokers.

CLINICAL FEATURES

The palate of patients with nicotine stomatitis is usually whiter than normal, exhibiting multiple, small circular papules with tiny umbilicated red centers on the hard palate (Figure 6-23). The white background may exhibit an irregular surface (fissured or wrinkled). Lesions may also be seen on the buccal mucosa, particularly on the same side of the mouth that the pipe or cigar is held.

HISTOPATHOLOGY

A biopsy of one of the umbilicated papules reveals a hyperkeratosis and acanthosis of the surface epithelium and a dilated salivary gland duct exhibiting squamous metaplasia of the ductal lining. The connective tissue adjacent to the salivary gland duct exhibits variable degrees of chronic inflammation (Figure 6-24).

TREATMENT

Nicotine stomatitis does not appear to predispose the hard palate to malignancy. However, some authors suggest that the degree of smoking that causes nicotine



FIGURE 6-23

Nicotine stomatitis. The palate is whiter than normal and exhibits multiple small raised nodules with red umbilicated centers, particularly on the soft palate.

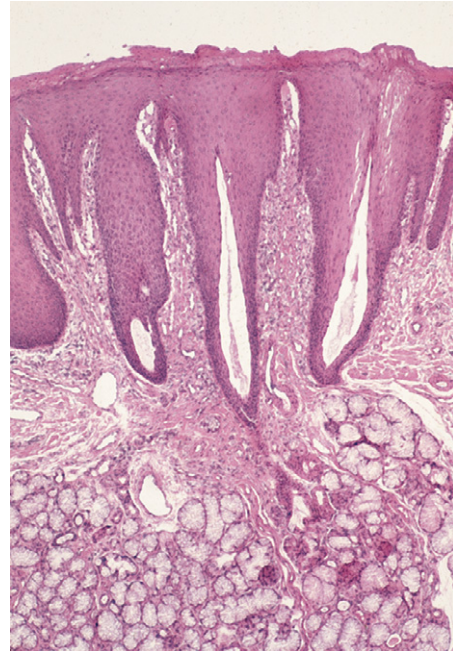


FIGURE 6-24

Nicotine stomatitis. The microscopic features of the small nodules reveal widened excretory ducts of minor salivary glands in which extensive squamous metaplasia of the normal cuboidal cells exists.

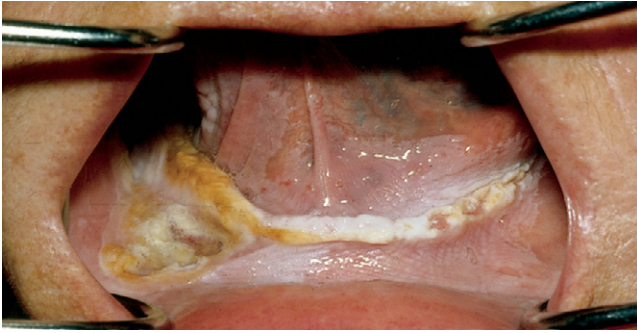
stomatitis in the more anterior oral tissues also increases the risk of developing squamous cell carcinoma of the faucial and retromolar regions of the mouth and of the upper and lower respiratory tract. Nicotine stomatitis rapidly resolves when the smoking habit stops.

PROLIFERATIVE VERRUCOUS LEUKOPLAKIA

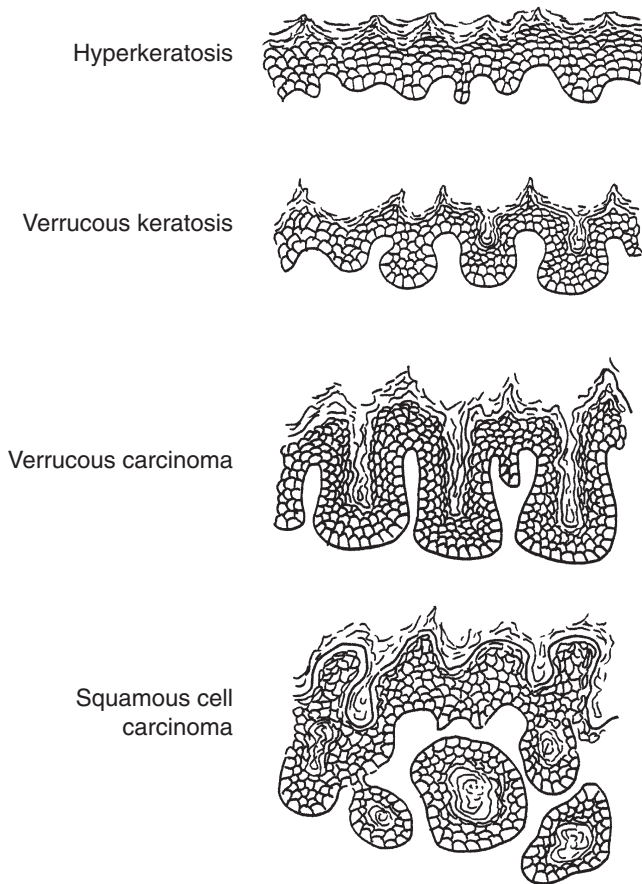
PROLIFERATIVE VERRUCOUS LEUKOPLAKIA: Diffuse white and/or papillary (“warty”) areas of the oral mucosa resulting from varying degrees of epithelial hyperplasia; has the potential to develop into verrucous carcinoma or well-differentiated squamous cell carcinoma.

Proliferative verrucous leukoplakia (PVL) is a recently delineated entity that occurs primarily in older patients, with a strong predilection for women (4:1 female-to-male ratio). It is described as multiple areas of diffuse leukoplakia with varying degrees of whiteness and a surface texture consisting of both smooth and warty areas (Figure 6-25). The clinical course of PVL is relatively slow but with a relentless progression to squamous cell carcinoma. In most cases, no identifiable causative factors can be found.

The term *verrucous hyperplasia* is sometimes used to define a similar benign, largely exophytic type of

**FIGURE 6-25**

Proliferative verrucous leukoplakia. Both quadrants of the mandibular alveolar ridge are covered with a diffuse white lesion with some areas extensively thickened with a warty, friable surface. Fainter white areas extend into the buccal vestibule.

**FIGURE 6-26**

Proliferative verrucous leukoplakia. The spectrum of histologic changes. Lesions slowly enlarge while progressing from the mildest form of hyperkeratosis through a stage of verrucous keratosis to verrucous carcinoma, with some lesions eventually becoming well-differentiated squamous cell carcinoma.

undulating epithelial hyperplasia that if left untreated may or may not progress to a verrucous carcinoma. Its relationship to PVL is not completely understood but is believed to represent part of the spectrum of change found in that entity.

HISTOPATHOLOGY

The microscopic appearance of PVL exhibits a wide spectrum of the changes within the realm of epithelial hyperplasia. The changes range from mild forms of hyperorthokeratosis to verrucous carcinoma. Some cases that were followed for long periods have developed focal areas of well-differentiated squamous cell carcinoma (Figure 6-26).

TREATMENT

During the early stages, when lesions are small, treatment of PVL consists of local surgical excision. During later stages, when lesions can extend to involve an entire arch or both arches, treatment becomes more difficult. In the maxilla, involvement of the soft palate, uvula, and tonsillar pillars can be problematic. In these areas the difficulty of surgical excision is related to the diffuse nature of the lesions and their proximity to structures that need to remain intact to enable mastication and speech. Recent refinements in the use of laser therapy have been helpful in arresting the progression of the disease process while preserving the vital anatomic structures.

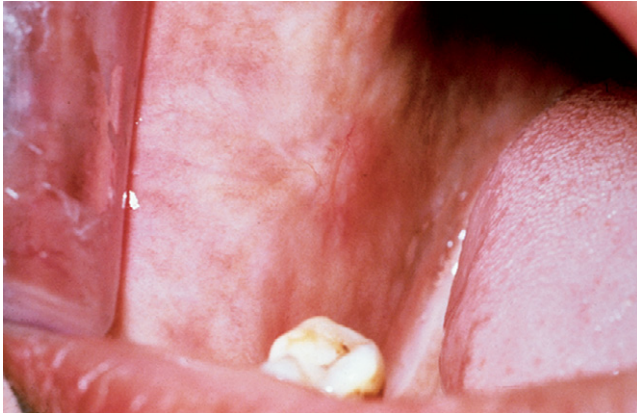
EPITHELIAL ATROPHY

EPITHELIAL ATROPHY: *Reduction in the normal thickness of epithelium that involves less than the entire thickness of the epithelium.*

Although hyperkeratosis usually occurs on the surface of normal or hyperplastic epithelium, it can also occur in association with atrophic epithelium. When a leukoplakia exhibits hyperkeratosis on the surface of atrophic epithelium, it is generally considered to be at greater risk of progressing to premalignancy (epithelial dysplasia) or malignancy than hyperkeratosis on the surface of normal or hyperplastic epithelium. Such an event commonly occurs on the lower lip of patients with prolonged actinic (solar) cheilitis before the development of squamous cell carcinoma.

ORAL SUBMUCOUS FIBROSIS

ORAL SUBMUCOUS FIBROSIS: *Diffuse firm whitish areas of submucosal scarring usually caused by frequent and prolonged contact with betel nut quids, tobacco, or hot chili peppers; lesions have a higher than normal risk of developing squamous cell carcinoma.*

**FIGURE 6-27**

Oral submucous fibrosis. The buccal mucosa is pale and firm as the result of the underlying fibrosis of the normally loose and soft connective tissue.

Oral submucous fibrosis is a disorder that resembles scleroderma, except that it is limited to the oral cavity. The disease occurs primarily in India, Pakistan, and Burma, but cases also occur in China, Thailand, Nepal, and Vietnam. Although the exact cause of the disease remains unknown, it has been suggested that it probably results from a hypersensitivity to eating hot peppers (chilies), from betel nut chewing, or from protracted tobacco use. The atrophic epithelium in oral submucous fibrosis is at increased risk of progressing to premalignancy and malignancy than is normal epithelium.

CLINICAL FEATURES

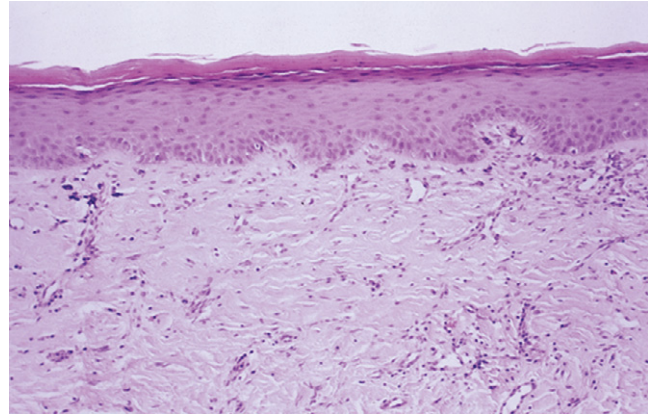
Oral submucous fibrosis affects the oral tissue of the buccal mucosa, lips, soft palate, and occasionally the pharynx. The tissue is symmetrically affected and becomes progressively firm and pale. A common complaint is a progressive stiffness of the cheeks, which inhibits the ability to open the mouth. The oral mucosa appears pale and atrophic (Figure 6-27).

HISTOPATHOLOGY

The earliest stage of the disease is characterized by chronic inflammation of the submucosal connective tissue. This stage is followed by a diffuse progressive fibrosis and atrophy of the overlying epithelium (Figure 6-28). The atrophic epithelium has a greater tendency to develop hyperkeratosis and epithelial dysplasia, which can progress to squamous cell carcinoma. For these reasons oral submucous fibrosis is considered a precancerous condition.

TREATMENT

Oral submucous fibrosis is usually diagnosed when the disease is at an advanced stage and lesions are widespread. At this stage surgical treatment is usually not

**FIGURE 6-28**

Oral submucous fibrosis. The overlying epithelium is thinned (atrophic), and the submucosa is composed of a dense fibrous connective tissue with a reduced vascularity.

possible, but systemic and intralesional injections of corticosteroids have been used with some success.

EPITHELIAL DYSPLASIA

EPITHELIAL DYSPLASIA: A premalignant change in epithelium characterized by a combination of cellular and architectural alterations.

The development of a malignancy in stratified squamous epithelium occurs spontaneously or as a gradual process in which multiple minor individual cellular and tissue alterations eventually culminate in frank malignancy. The combination of cellular and architectural changes observed in the gradual transition to malignancy (premalignancy) is termed *epithelial dysplasia*.

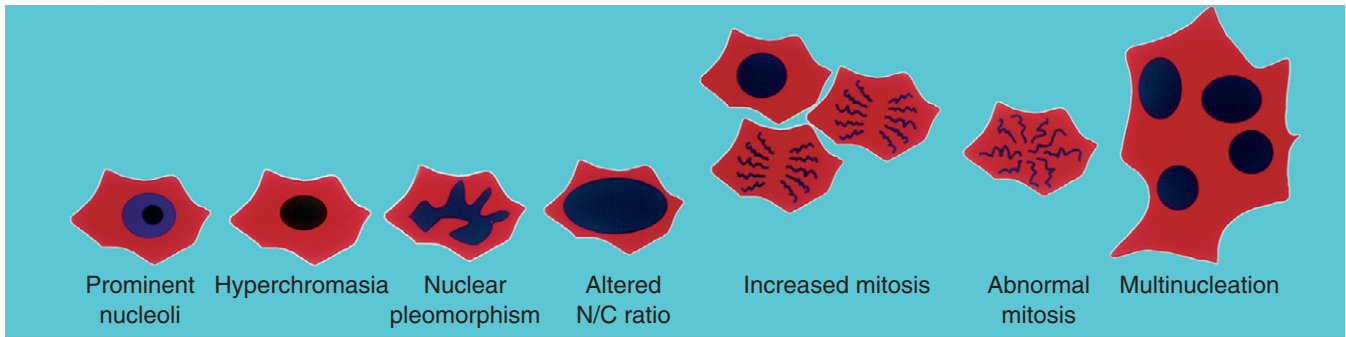
Individual cell alterations (Figure 6-29) found in epithelial dysplasia include the following:

1. Prominent nucleoli
2. Hyperchromatic nuclei (hyperchromasia)
3. Nuclear pleomorphism
4. Altered nuclear:cytoplasmic ratio
5. Increased mitotic activity
6. Abnormal mitotic figures
7. Multinucleation of cells (poikilocarynosis)

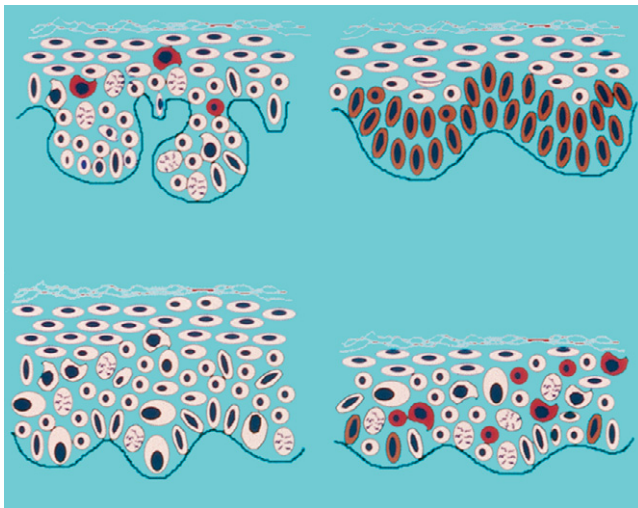
Architectural alterations (Figure 6-30) include combinations of the following:

1. Formation of bulbous rete pegs
2. Basilar hyperplasia
3. Hypercellularity
4. Altered maturation pattern of keratinocytes

The clinical appearance of epithelial dysplasia is most frequently observed as an area of leukoplakia (Figure 6-31) that is similar to other more innocuous-appearing white lesions.

**FIGURE 6-29**

Individual cell alterations found in epithelial dysplasia. The degree of severity of an epithelial dysplasia is determined, in part, by the frequency and combination of these alterations.

**FIGURE 6-30**

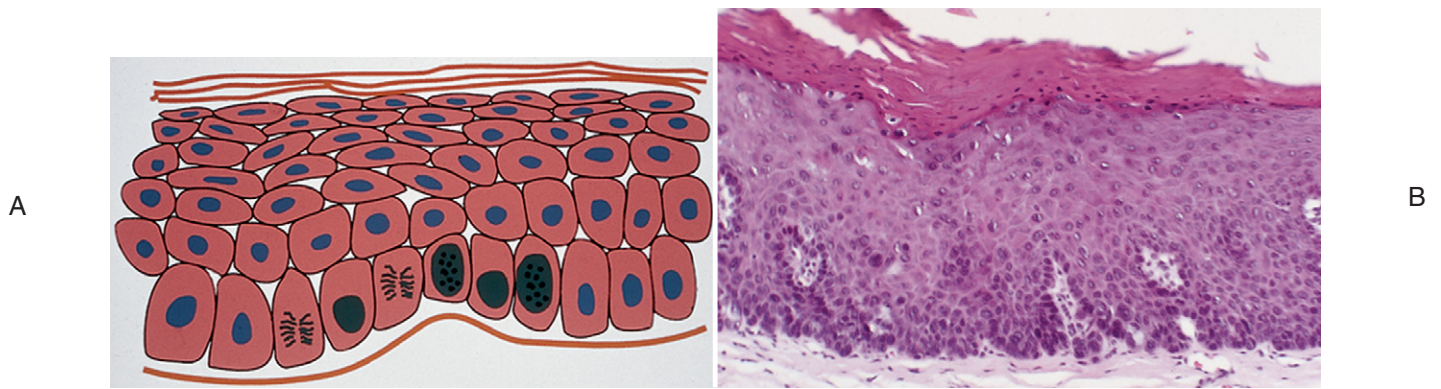
Architectural alterations of the epithelium found in epithelial dysplasia. The degree of severity of the epithelial dysplasia is determined by the extent of these alterations combined with the individual cell abnormalities.

The degree of severity of an epithelial dysplasia is conveyed by assigning one of three grades—mild, moderate, or severe—based on its microscopic features (Figures 6-32 through 6-34). It is important to note that the grade of an epithelial dysplasia can increase (become worse) with time. An epithelial dysplasia of the floor of the mouth or lateral border of the tongue in a cigarette smoker will, with time and continued smoking, progressively increase its grade from mild to moderate and, eventually to severe. The rate at which epithelial dysplasia will progress from its mildest to its most severe forms will vary considerably among individuals and may range from months to years. It is important to note that some

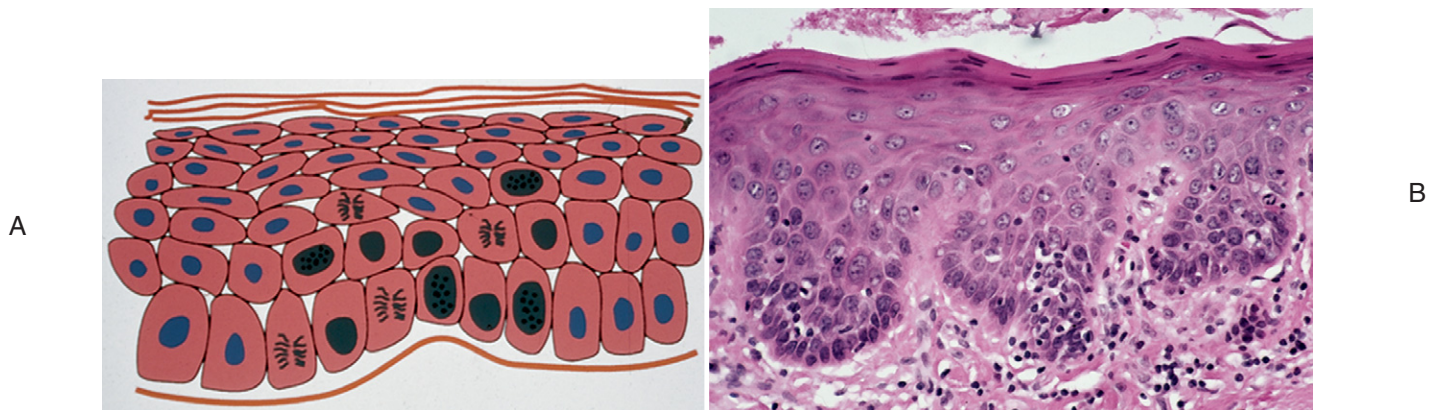
**FIGURE 6-31**

Epithelial dysplasia. The leukoplakic area on the ventral surface of the tongue is a common presentation of epithelial dysplasia in the oral cavity.

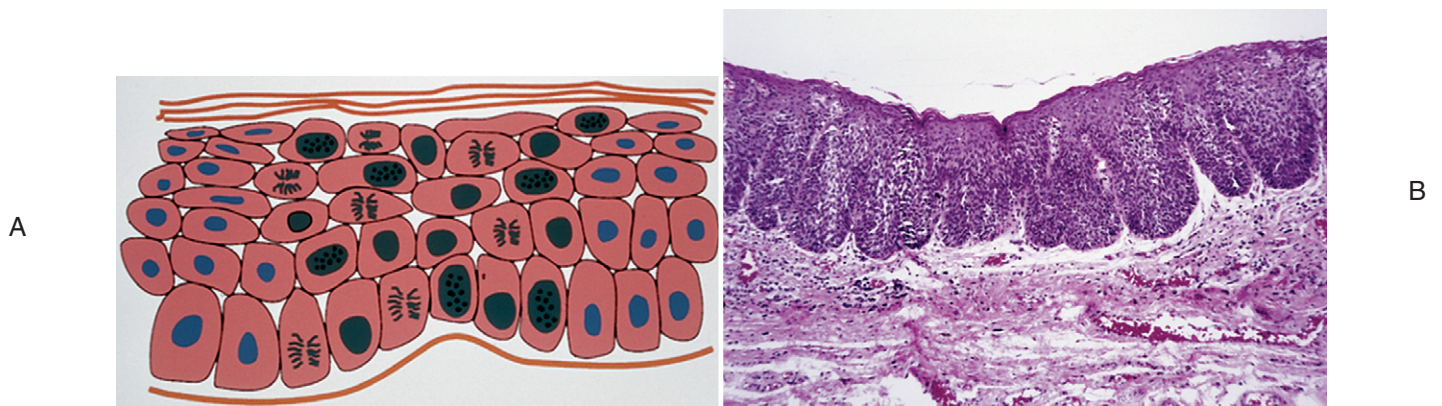
mild and incipient forms of epithelial dysplasia will regress (reverse), and the epithelium will revert to normal when the inciting factor is removed (i.e., when the patient stops smoking). In other forms of epithelial dysplasia, reversal may not be possible, even after the removal of the causative factor. In some cases, removal appears to slow the rate of progression to a more severe form. It appears doubtful that the moderate and severe forms of epithelial dysplasia can regress by simply removing the causative factor. When the dysplastic cells breach the basement membrane and enter the adjacent connective tissue, it is considered to be a superficially invasive or microinvasive squamous cell carcinoma.

**FIGURE 6-32**

A, Mild epithelial dysplasia. **B**, Microscopic appearance of mild epithelial dysplasia.

**FIGURE 6-33**

A, Moderate epithelial dysplasia. **B**, Microscopic appearance of moderate epithelial dysplasia.

**FIGURE 6-34**

A, Severe epithelial dysplasia. **B**, Microscopic appearance of severe epithelial dysplasia.

Areas of epithelial dysplasia often exhibit a chronic lymphocytic infiltrate in the adjacent connective tissue, and lymphocytes extend into the deeper layers of the dysplastic epithelium. If the dysplasia is mild and the lymphocytic infiltrate is intense, the potential exists for an

erroneous diagnosis. An epithelial dysplasia with an associated dense infiltrate of lymphocytes bears a striking resemblance to lichen planus, a common benign dermatologic and mucosal disorder. When an epithelial dysplasia has multiple histologic features in common with lichen

planus, it has been termed *lichenoid dysplasia*. Because there have been documented cases in which an intraoral squamous cell carcinoma has developed in the same site as lesions that had previously been diagnosed as lichen planus, the question remains whether the initial lesion was, in fact, a dysplasia with associated microscopic features similar to those of lichen planus or was a true lichen planus lesion. Recent studies of the epithelium from cases of lichen planus using genetic markers suggest that oral lichen planus did not have the genetic pathways usually associated with the development of epithelial dysplasia. Additional research will be needed using additional genetic markers on both lichen planus and a wide variety of epithelial dysplasias and squamous cell carcinomas to shed additional light on this important question. (See Chapter 8 for additional discussion.)

CARCINOMA IN SITU

CARCINOMA IN SITU: *The most severe stage of epithelial dysplasia, involving the entire thickness of the epithelium, with the epithelial basement membrane remaining intact.*

Carcinoma in situ (CIS) is the most severe form of epithelial dysplasia and involves the entire thickness of the epithelium (top-to-bottom change). It is cytologically similar to squamous cell carcinoma except that architecturally the epithelial basement membrane remains intact and no invasion into the connective tissue has occurred. When dysplastic epithelial cells breach the basement membrane and spread (invade) into the connective tissue, allowing for the possibility of distant metastasis to occur, CIS becomes squamous cell carcinoma.

ERYTHROPLAKIA

ERYTHROPLAKIA: *A clinical term for a red patch of the oral mucosa, frequently caused by epithelial dysplasia, carcinoma in situ, or squamous cell carcinoma.*

Erythroplakia, also termed *erythroplasia*, was first used by Queyrat to describe a red, velvety lesion on the glans penis of older men. Literally, the term means *a red patch or plaque*. The term is used to describe red mucosal lesions of the oral cavity that have no apparent cause.

CLINICAL FEATURES

Erythroplakia of the mouth is usually an asymptomatic lesion that occurs primarily in older males who smoke cigarettes. It can be found on the floor of the mouth (Figure 6-35), lateral and ventral surfaces of the tongue, soft palate, and buccal mucosa.

The term *speckled erythroplakia* is often used to describe a lesion that is primarily red but exhibits interspersed focal white plaques (Figure 6-36). This lesion should be viewed with a high degree of suspicion, be-

cause it has a high incidence of premalignant or malignant change. When obtaining a biopsy of this lesion, both red and white areas should be sampled.

HISTOPATHOLOGY

The microscopic evaluation of erythroplakia reveals that 60% to 90% are epithelial dysplasias, CIS, or squamous cell carcinomas. Consequently, oral erythroplakia should be viewed with a high degree of suspicion and routinely biopsied for histopathologic evaluation.

Three microscopic features of erythroplakia explain the deep-red coloration of the lesions: First, erythroplakia



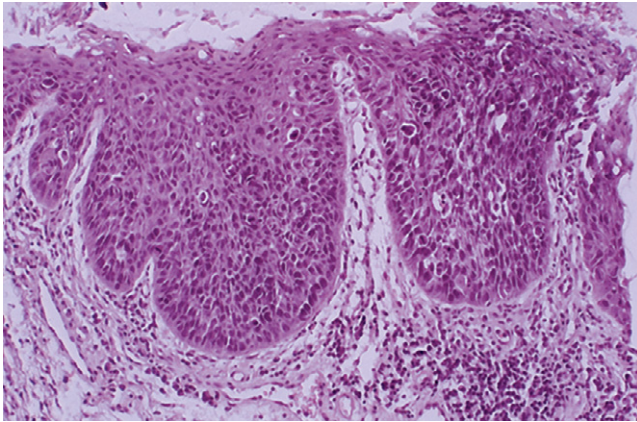
FIGURE 6-35

Erythroplakia. The red, slightly nodular area of the right anterior floor of the mouth is a common presentation of this clinical entity.



FIGURE 6-36

Speckled erythroplakia. The lesion in the right commissural area of the buccal mucosa exhibiting scattered white plaques against an erythematous background is a common presentation of dysplasia or early squamous cell carcinoma.

**FIGURE 6-37**

Carcinoma in situ. The microscopic alterations of the epithelium are severe. Areas of thickened epithelium that are adjacent to atrophic areas have inflamed connective tissue containing large vascular spaces. These microscopic features are responsible for the clinical appearance observed in erythroplakia or speckled erythroplakia.

lacks the surface layer of keratin that normally diffuses the redness emanating from the underlying vasculature. Second, the remaining epithelial layers that normally cover the connective tissue papillae between the rete pegs are frequently reduced in thickness; therefore the blood vessels normally present in the papillae are more visible from the surface than in normal mucosa. Third, in most erythroplakias, the size and number of vascular structures increase in response to the inflammation associated with the thinned and neoplastic epithelium (Figure 6-37).

TREATMENT

It is important that all erythroplakic lesions be biopsied to determine their exact nature. The treatment of erythroplakias depends on the specific histopathologic diagnosis of each case. Dysplasia and CIS are treated by local excision. Squamous cell carcinoma is treated more aggressively, depending on the clinical staging of the lesion.

MALIGNANT EPITHELIAL NEOPLASMS

SQUAMOUS CELL CARCINOMA

SQUAMOUS CELL CARCINOMA: *A malignant neoplasm of stratified squamous epithelium that is capable of locally destructive growth and distant metastasis.*

Squamous cell carcinoma, sometimes termed *epidermoid carcinoma*, is defined as a malignant neoplasm that is derived from or exhibits the morphologic features of

squamous epithelium. As discussed earlier, squamous cell carcinoma is often the end stage of a series of alterations in stratified squamous epithelium, beginning as an epithelial dysplasia and progressing until the dysplastic epithelial cells breach the basement membrane and invade into the connective tissue. It can also arise de novo from the overlying stratified squamous epithelium, having a relatively short premalignant phase.

Oral malignancies represent approximately 3% of all cancers in males and approximately 2% in females. The overall survival rate of patients with oral malignancies is approximately 50%. They are responsible for 2% of the annual deaths in males and 1% in females. Each year approximately 30,000 new cases of oral cancer are diagnosed in the United States. The incidence of oral cancer differs significantly, depending on the tobacco habits prevalent in the various countries throughout the world. The incidence of oral cancer increases significantly in societies where extensive tobacco use begins early in life and is continuous into adulthood.

Squamous cell carcinoma is by far the most common malignant neoplasm of the oral cavity, representing approximately 90% of all oral cancers. Although it occurs in various oral sites, it is most common on the lower lip, lateral borders of the tongue, and the floor of the mouth. The incidence of squamous cell carcinoma increases with age; most cases occur after 40 years of age.

A number of causative factors have been implicated in the development of oral squamous cell carcinoma. These

BOX 6-2

Causative Factors Associated with Oral Squamous Cell Carcinoma

SMOKED TOBACCO

Cigarettes
Cigars
Pipe

SMOKELESS TOBACCO

Snuff
Chewing tobacco
Quid (Pan)

ACTINIC RADIATION

INFECTIONS

Human papilloma virus (HPV)
Epstein-Barr virus (EBV)
Human immunodeficiency virus (HIV)
Candida albicans
Treponema pallidum

CHRONIC IRRITATION

ALCOHOL CONSUMPTION

include tobacco habits, alcohol consumption, viruses, actinic radiation, immunosuppression, nutritional deficiencies, preexisting diseases, and chronic irritation (Box 6-2).

Squamous cell carcinoma of the head and neck occurs when sufficient gene alterations irreversibly alter the normal regulation of cell division and apoptosis. This results in a new rapidly growing tissue that requires additional blood supply to thrive. Identification of the genes and proteins that regulate cell division, apoptosis, and angiogenesis are key to the development of diagnostic tools that can predict transition to malignant disease before it occurs, the development of treatments that specifically target only lesional tissue, and the determination of long-term outcome (prognosis).

The molecular basis of oral carcinogenesis is still evolving. Based on current research findings, several mechanisms, alone or in combination, have been hypothesized (Figure 6-38). The basal cells of oral epithelium normally have a relatively high rate of mitotic activity. Abnormal acceleration of their cell cycles is one of the hallmarks of carcinogenesis. Cells can be stimulated to divide when growth factors are secreted by adjacent cells (paracrine) or even by the same cell (autocrine). These factors may cause a disturbance

in the quality or quantity of the cell-regulating proteins and occasionally may induce unregulated growth. The growth factors bind to cell surface receptors, evoking *kinase* activity within the cytoplasm adjacent to the binding region. By using the signal transduction biochemical pathway, the growth factors progress to activate transcription factors. These targeted genes generate proteins (*cyclins*) that activate the cell cycle sometimes in an unregulated manner. The specific gene loci responsible for producing proteins that can upset the replication cycle of cells are termed *oncogenes*, and their protein products are termed *oncoproteins*. When oncogenes are stimulated to overproduce proteins that stimulate continuous mitosis ("up regulation"), the result is neoplastic growth. Alteration in the oncogene activity has been associated with one or more of the environmental factors (co-factors) mentioned in the following section. The activated cyclins and cyclin-dependent kinases (CDKs) phosphorylate pocket proteins, such as *pRB*, and release *E2F* transcription factor from its binding site. This results in the synthesis of mitotic-promoting proteins that move the cell through the G1/S and G2/M checkpoints.

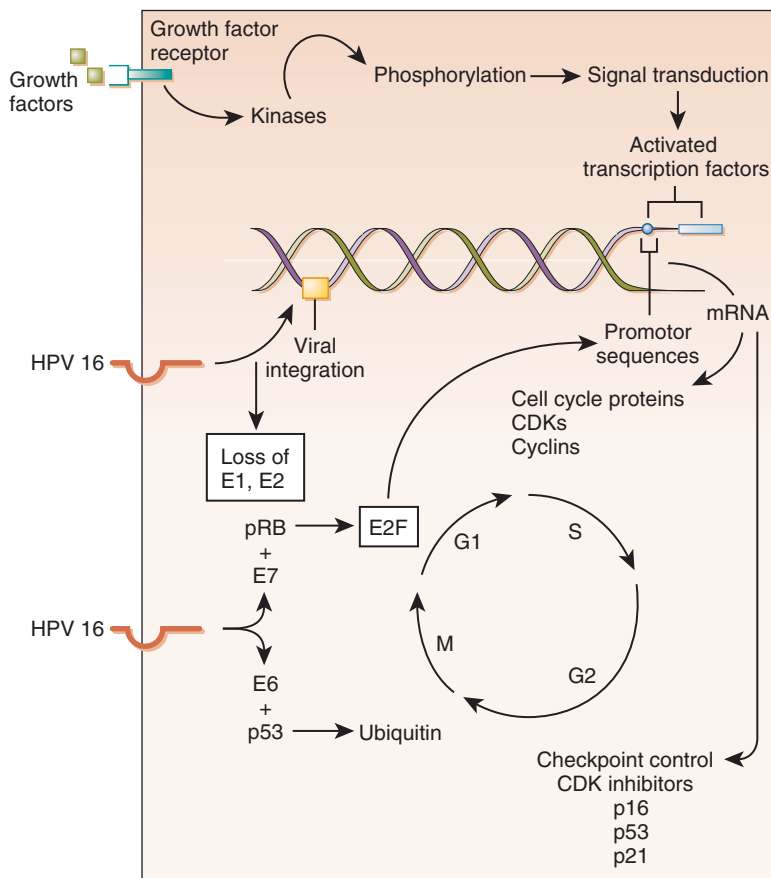


FIGURE 6-38

Possible mechanisms of carcinogenesis as a result of abnormal acceleration of cell cycle based on current research. Growth factors via intracytoplasmic kinase activity trigger DNA transcription factors that accelerate the cell cycle. Additionally, viral agents such as HPV 16 may inhibit the normally present tumor-suppressor proteins and promote the cell cycle proteins, altering the normal balance of the cell cycle (see text for more details).

Normally, the cell replication cycle is monitored and regulated by *tumor-suppressor proteins* (TSPs) that are able to arrest the cell cycle and even lead the cell to programmed death (*apoptosis*). The TSPs *p16*, *p53*, and *p21* are known to arrest abnormal progression of the cell cycle. Oral cancers exhibit a high propensity for mutations in the suppressor genes with resultant defective TSP function and over-activation of the cell cycle.

Human papillomavirus type 16 (HPV 16) has been identified in some oral carcinomas. Its early genes (E1, E2) are lost when the HPV oncogenes E6 and E7 become integrated into the host cell genome. E2 serves as a control element for E6 and E7 transcription, and its loss abrogates the negative control of expression of these oncoproteins. Additionally, HPV E6 binds *p53* initiating its degradation through the *ubiquitin* enzymatic pathway, removing the control on cell cycling while HPV E7 binds to *pRB* with release of E2F, promoting cell cycling. HPV alone is not sufficient for oncogenesis; mutations in suppressor genes and activation of other oncogenes are also required for tumor suppressor genes, and activation of other oncogenes are also required for tumor formation (Figure 6-39).

Carcinogenic Factors

Although the exact manner in which the following environmental factors or cofactors interact and interfere with the cell signaling and cycling mechanisms is un-

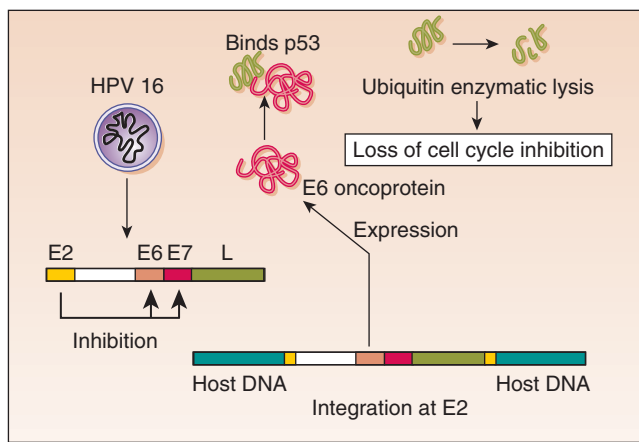


FIGURE 6-39

A carcinogenic infectious agent. Human papilloma virus (HPV) 16 infects a keratinocyte. Normally the E2 protein inhibits expression of E6 and E7. When the HPV virus integrates into the host DNA at the E2 site, it causes the E2 protein to fail to be expressed and both E6 and E7 to be overexpressed. The overexpressed HPV E6 oncoprotein binds to *p53*, causing it to be downgraded with resultant loss of cell cycle inhibition. Mitotic activity then increases in the infected cell.

known, they are associated with an increased incidence of oral squamous cell carcinoma.

Tobacco

The habitual use of tobacco in its various forms, which consists primarily of cigarettes, cigars, pipe tobacco, and quid, has been reported to be the most important factor associated with the transformation of normal mucosal epithelial cells to squamous cell carcinoma. Snuff and chewing tobacco have also been implicated (Figure 6-40). Research indicates that 8 of every 10 patients with oral cancer are long-term, heavy smokers. As a carcinogen, smoked tobacco seems to be more potent than smokeless tobacco. The association between tobacco use and cancer is further observed in patients who have received treatment for oral squamous cell carcinoma. Research indicates that 30% to 37% of patients who con-

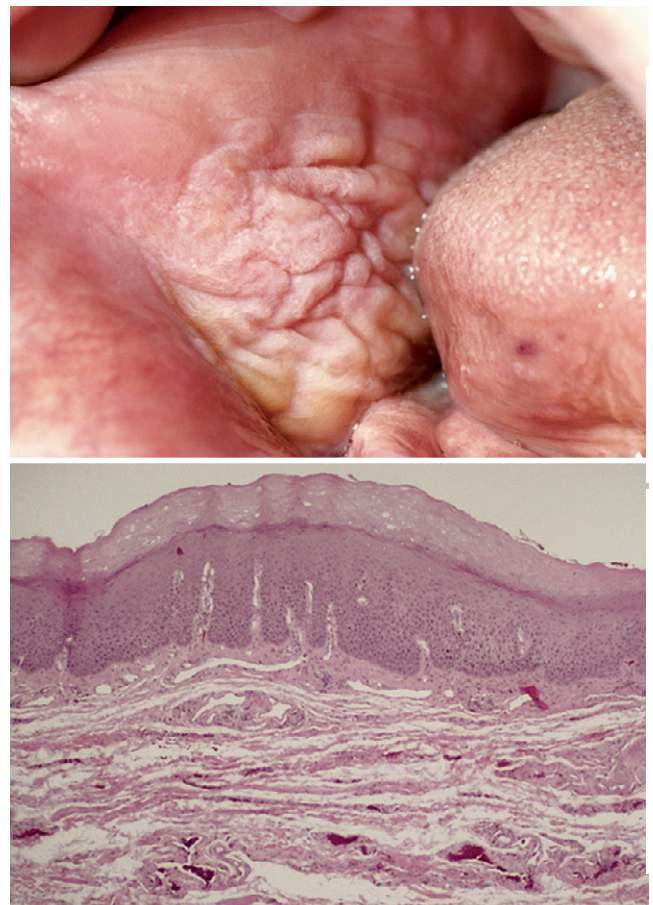


FIGURE 6-40

Tobacco chewer's pouch. **A**, Lesion of posterior vestibule and buccal mucosa with characteristic wrinkles and leukoplakic appearance. **B**, Microscopic appearance reveals a thickened layer of orthokeratin, acanthosis, and an undulating surface.

tinue to smoke after treatment for oral cancer develop a new lesion in another oropharyngeal site, whereas only 6% to 13% of those who quit smoking develop new lesions.

Actinic Radiation

Light-skinned individuals whose skin does not tan well and who sustain prolonged occupational or recreational exposure to direct sunlight are at greater risk of developing squamous cell carcinoma of the lower lip. The epithelium of the lip undergoes a series of pre-neoplastic changes that become progressively worse as the dose of actinic radiation accumulates and the patient ages. The sharp ridge or line of demarcation at the vermilion and cutaneous junction on the lower lip is replaced by a puffy, rounded margin, and the skin develops multiple vertical creases. The exposed mu-

cosal surface becomes mottled, consisting of red (atrophy) and white (hyperorthokeratosis) patches, and displays prominent superficial blood vessels (telangiectasia). This accumulation of changes is termed **actinic cheilitis** (also termed *solar cheilosis*, *solar keratosis*, or *solar elastosis*) (Figure 6-41). As time and exposure progress, recurring chronic ulcers frequently develop on the lip, usually lateral to the midline. Eventually the ulcers stop healing, at which point a biopsy usually reveals that a superficial well-differentiated squamous cell carcinoma has developed. Treatment of the altered tissue before the development of malignancy usually consists of superficial surgical removal of the damaged tissue (lip stripping, lip shave). When biopsy reveals the presence of invasion, surgical wedge resection is usually adequate treatment unless metastasis has occurred.

Infections

Various infectious agents such as bacteria (syphilis) and fungi (chronic candidiasis) have been implicated as predisposing factors for oral squamous cell carcinoma. Convincing evidence firmly linking these agents to the development of squamous cell carcinoma has not been found. More substantial evidence of a link with an infectious agent has occurred with some viral agents. The most convincing is the association of the various genotypes of human papilloma virus (HPV) to anogenital squamous cell carcinoma. Although the mechanism has not yet been completely elucidated, it is reported that the HPV early gene products E6 and E7 bind the host keratinocyte suppressor gene proteins p53 and/or RB, thus allowing uncontrolled cell cycling. Also shown is that viral E6 and E7 oncoproteins may also induce overexpression of the EGF-R (see Figure 6-39).

Because it is difficult to isolate HPV 16 and HPV 18 in squamous cell carcinoma of the head and neck, compared with isolating them in cervical carcinoma, research has yet to establish as convincing a link between oral lesions and HPV as occurs in lesions of the anogenital region.

Immunosuppression

Acquired immunodeficiency syndrome (AIDS) predisposes relatively young individuals to various oral and nonoral malignancies. Intraoral squamous cell carcinoma is among the malignant lesions that occur more frequently in AIDS patients. It occurs at a much younger age than in the general population and without the usual causative factors. Oral Kaposi's sarcoma and lymphoma, which also occur at a younger age in AIDS patients, are much more common than squamous cell carcinoma.

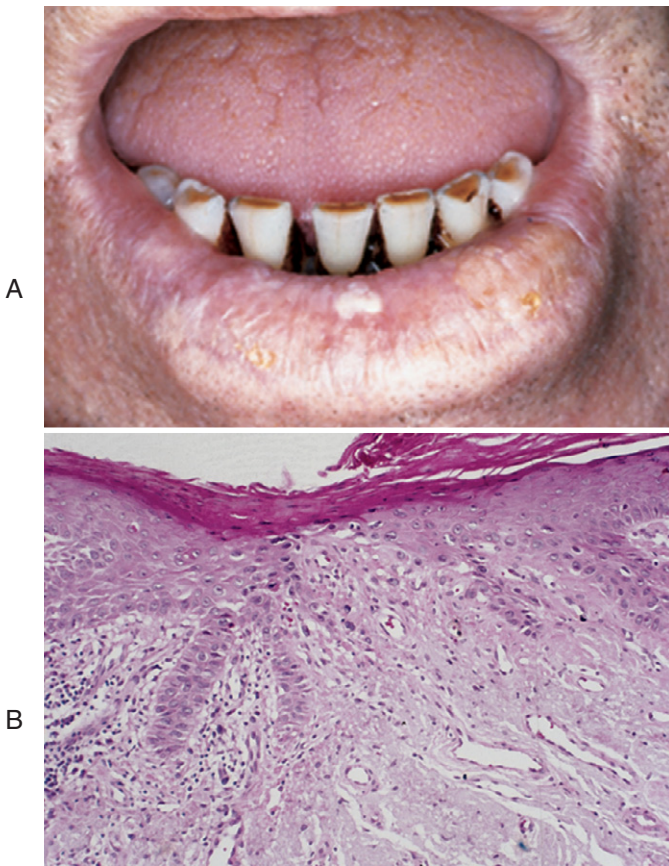


FIGURE 6-41

Actinic cheilitis. **A,** The lower lip is puffy, with loss of the distinct vermilion border, and mottled with leukoplakic and atrophic areas. **B,** Microscopic features include hyperorthokeratosis, epithelial atrophy, dysplasia, basophilic degeneration of collagen, and telangiectasia.

Nutritional Deficiencies

Patients with chronic iron deficiency anemia (Plummer-Vinson syndrome) develop epithelial atrophy of the gastrointestinal tract, including that of the oral cavity, and have an increased susceptibility to esophageal and oral carcinomas. A direct causal relationship between low serum iron levels or other mineral deficiencies and cancer development has not been established.

Preexisting Oral Diseases

Oral submucous fibrosis (discussed earlier in this chapter) predisposes the oral mucosa to develop squamous cell carcinoma. Although some indication exists that chronic forms of oral lichen planus also predispose the oral mucosa to develop squamous cell carcinoma, this factor is still being debated (see Chapter 8).

Co-Factors

Although not considered direct causes, several co-factors (e.g., alcohol consumption, chronic irritation caused by ill-fitting dentures) have been implicated in the progression of oral squamous cell carcinoma. The evidence for a direct topical effect by orally ingested alcohol is lacking, because most chronic alcohol drinkers are also smokers.

Most investigators believe that the effect of alcohol on the induction of oral cancer is indirect, possibly related to liver damage (cirrhosis) and an inability to detoxify the blood constituents. The association between cirrhosis of the liver and squamous cell carcinoma of the floor of the mouth and tongue is especially high. When high alcohol intake is combined with heavy smoking, a synergistic effect is possible that may greatly increase the incidence of oropharyngeal carcinoma.

CLINICAL FEATURES

Oral squamous cell carcinoma has a number of different clinical presentations. The most common early presentations of intraoral squamous cell carcinoma are leukoplakias and erythroplakias. The more advanced lesions may first appear as a painless ulcer, a tumorous mass, or a verrucous (papillary) growth. Squamous cell carcinoma that has infiltrated deep into the connective tissue may have few surface changes but appears as a firm indurated area with associated loss of tissue mobility. On the floor of the mouth this commonly causes fixation of the tongue or inability to fully open the mouth. Carcinoma that arises from the gingiva and invades into the underlying bone of the mandible or maxilla can result in loosening or loss of teeth, whereas carcinoma that penetrates deeply into the mandible with involvement of the inferior alveolar nerve can cause paresthesia of the teeth and lower lip.

HISTOPATHOLOGY

Squamous cell carcinoma is diagnosed by microscopic examination of a representative biopsy of the neoplastic tissue. Common to all lesions is the presence of invasion into the underlying connective tissue and the inherent potential of malignant cells to erode the lymphatic and blood vessel walls, allowing them to be transported to distant sites (metastasis) (Figure 6-42).

Although all carcinomas have some capacity for metastasis, considerable variation exists in the potential of individual squamous cell carcinomas to metastasize. This potential is correlated to some extent with the histologic variation found in oral squamous cell carcinoma. The histologic variation is related to the degree of differentiation (grade) exhibited by the tumor cells and how closely the tissue architecture resembles normal stratified squamous epithelium. Tumors that produce significant amounts of keratin and exhibit some features of maturation from basal cells to keratin are considered to be **well differentiated** (Figure 6-43). Tumors that produce little or no keratin but in which the epithelium is still recognizable as stratified squamous, despite its significant deviation

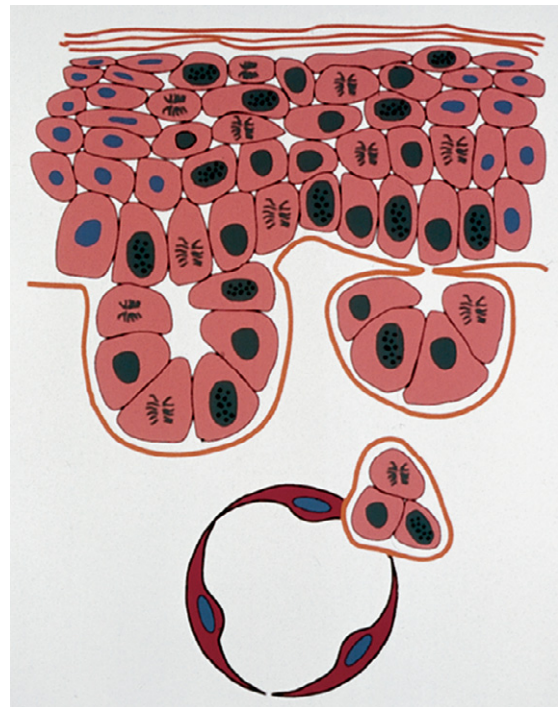
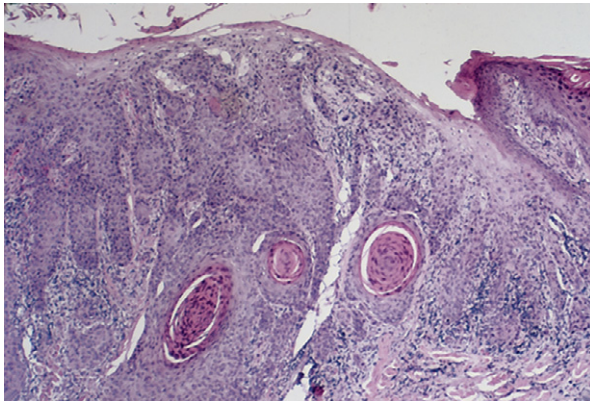
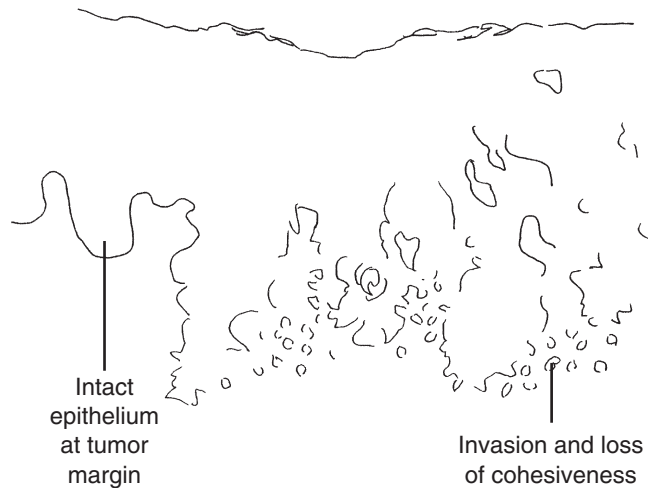
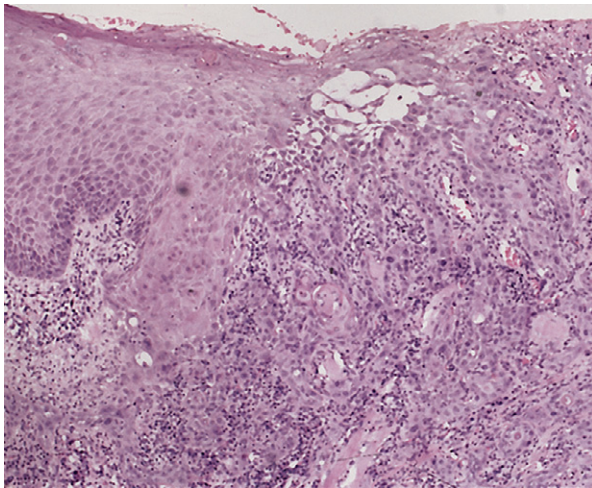


FIGURE 6-42

Transition of epithelial dysplasia to invasive squamous cell carcinoma. Malignant cells have penetrated through the basement membrane into the underlying connective tissue, where they are capable of eroding into lymphatic vessels.

**FIGURE 6-43**

Well-differentiated squamous cell carcinoma. Microscopic features reveal irregularly elongated rete pegs invading the connective tissue and containing aberrant accumulations of keratin (keratin pearls).

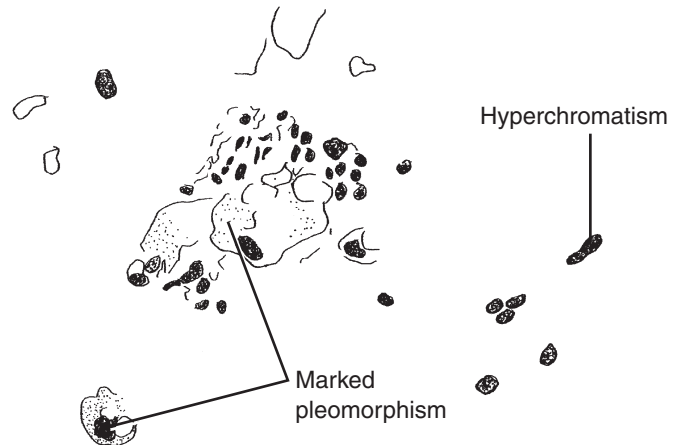
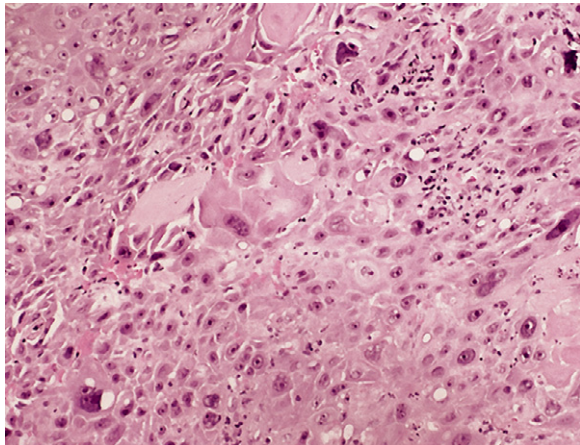
**FIGURE 6-44**

Moderately differentiated squamous cell carcinoma. The photomicrograph illustrates an abrupt line of demarcation between the normal epithelium (*left*) and the invasive neoplastic squamous epithelium that is nonkeratinized and exhibits loss of cellular cohesiveness.

from normal, are regarded as **moderately differentiated** (Figure 6-44). Tumors that produce no keratin, bear little resemblance to stratified squamous epithelium, exhibit a significant lack of normal architectural pattern and cohesiveness of cells, and exhibit extensive cellular abnormalities are designated as **poorly differentiated** (Figure 6-45).

As a general rule, squamous cell carcinomas of the lower lip tend to be well differentiated; those that oc-

cur on the lateral borders of the tongue are often moderately differentiated, and those that involve the tonsillar region tend to be poorly differentiated. Although a number of different factors, such as anatomic structures and lymphatic drainage patterns, influence the biologic behavior of a tumor, the degree of differentiation appears to be most important in determining its growth rate and ultimately its tendency to metastasize.

**FIGURE 6-45**

Poorly differentiated squamous cell carcinoma. The photomicrograph exhibits sheets of cells lacking an architectural pattern and exhibiting severe cellular abnormalities of hyperchromatism and pleomorphism.

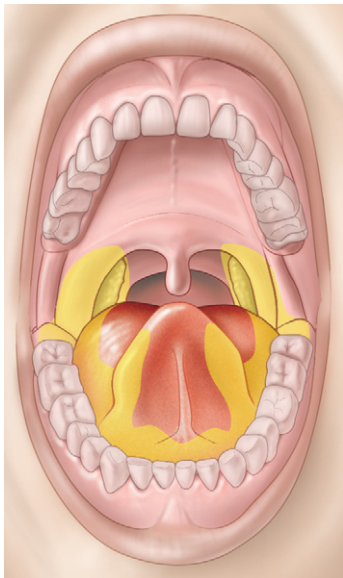
Sites and Incidence

The incidence of squamous cell carcinoma differs between anatomic sites. Some anatomic sites are relatively resistant, whereas others are particularly susceptible (Table 6-2). When all anatomic sites are considered, the lower lip is the most susceptible site. Within the confines of the oral cavity, the lateral and ventral aspects of the

tongue and the adjacent floor of the mouth are the most susceptible sites, followed by the posterior soft palate, particularly in the areas adjacent to the tonsillar pillars (Figure 6-46). Less frequently, the gingiva and alveolar ridge area is the site of origin. The buccal mucosa, especially above the occlusal line, is seldom involved. Compared with other intraoral sites, carcinomas arising on the hard palate and dorsum of the tongue are relatively rare.

Lower Lip

Squamous cell carcinoma of the lower lip accounts for 30% to 40% of all oral carcinomas. It is much more common in males than females, occurring most commonly in patients who are in their fifth to eighth decade of life. Most lesions occur on either the right or left vermillion borders (Figure 6-47) and seldom at the midline. In nearly all cases the lesions are preceded by a prolonged period of actinic cheilitis, followed by an interval of recurring ulceration and encrustation. Eventually the ulcer fails to heal and develops a rolled border surrounded by

**FIGURE 6-46**

Horseshoe-shaped intraoral area most prone to the development of squamous cell carcinoma. It consists of the anterior floor of the mouth, lateral borders of the tongue, tonsillar pillars, and lateral soft palate.

Table 6-2 Approximate Relative Incidence of Oral Carcinoma

Site	Relative Incidence
Lower lip	35
Lateral/ventral tongue	25
Floor of mouth	20
Soft palate	15
Gingival/alveolar ridge	4
Buccal mucosa	1



FIGURE 6-47
Squamous cell carcinoma of the lower lip.

indurated tissue. Squamous cell carcinomas of the lower lip are usually well differentiated and slow to metastasize. If metastases have not occurred, these lesions are nearly 100% curable. Lower lip lesions that have been present for prolonged periods of time usually metastasize to the regional submental lymph nodes and then to the digastric and cervical nodes.

Tongue

The lateral borders of the tongue (including the adjacent ventral surfaces) are the sites of 25% of all oral squamous cell carcinomas and 50% of intraoral lesions. The lateral borders of the tongue are part of the U-shaped area of oral mucosa that is at high-risk for the development of squamous cell carcinoma (see Figure 6-46). The other sites included in this area are the anterior, right, and left floor of the mouth and the retromolar pad and adjacent areas of the soft palate. The dorsum of the tongue and hard palate are relatively resistant to the development of squamous cell carcinoma, although extension from adjacent sites frequently occurs.

Early carcinomatous lesions arising on the lateral border of the tongue are usually located in the middle and posterior thirds (Figure 6-48). Commonly, lesions initially appear as an area of leukoplakia that eventually ulcerates and develops raised or rolled borders. Other lesions may begin as an area of erythroplakia or nodularity. Advanced lesions of all clinical types eventually ulcerate and produce extensive induration of the surrounding tissue, often resulting in pain, immobility, and altered speech. The initial appearance of some lesions makes it impossible to clinically separate them from chronic traumatic ulcers; a biopsy to determine their true nature is therefore required. Most lesions of the lateral border of the tongue are moderately differentiated squamous cell carcinomas. Metastasis commonly occurs early in the course of the disease and extends to the sub-



FIGURE 6-48
Squamous cell carcinoma of the lateral tongue.

mandibular and deep cervical lymph nodes. A partial glossectomy followed by radiotherapy is the treatment of choice. In general, the 5-year survival rate of patients with more advanced lesions is less than 30%.

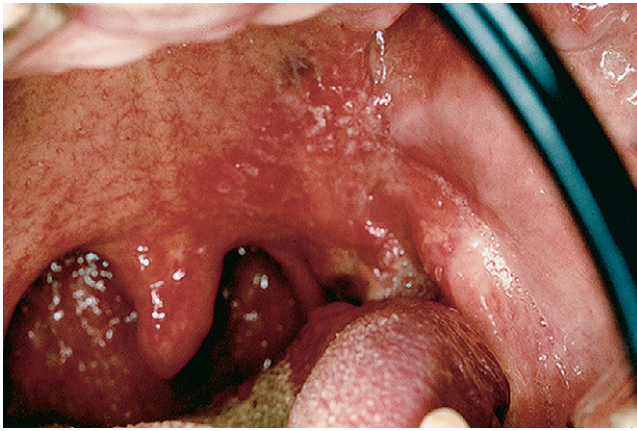
Floor of Mouth

The floor of the mouth is the site of approximately 20% of all oral carcinomas and the third most common site of all intraoral squamous cell carcinomas. Most lesions are located in the anterior areas adjacent to the caruncles containing the orifices of Wharton ducts. Patients commonly are long-time smokers, heavy alcohol drinkers, or both.

The clinical appearance of the early or initial lesions of the floor of the mouth commonly begins as an area of erythroplakia or speckled erythroplakia that gradually develops into an irregularly shaped central ulcer. As the lesion progresses, the area becomes nodular and indurated as the invasion involves the deeper tissues (Figure 6-49). In advanced lesions, fixation of the tongue and extension



FIGURE 6-49
Squamous cell carcinoma of the anterior floor of the mouth.

**FIGURE 6-50**

Squamous cell carcinoma of the left soft palate arising in an area of speckled erythroplakia.

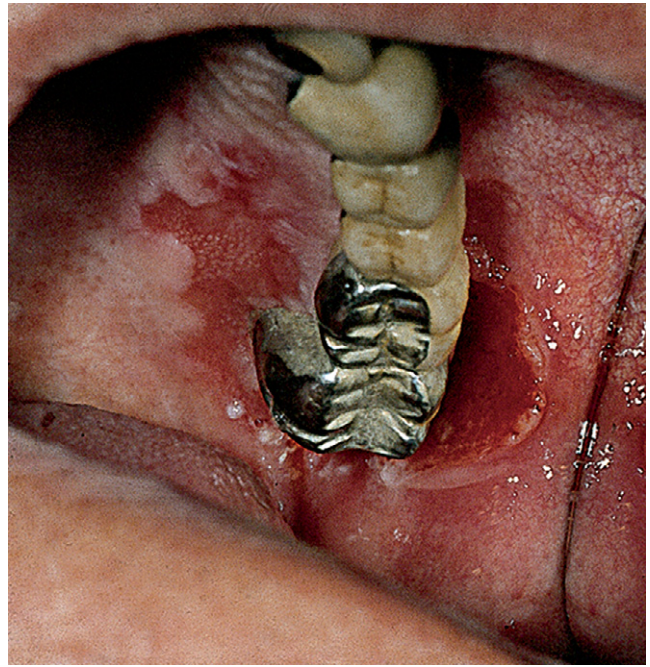
onto the gingiva are common. Most lesions in this area are moderately differentiated, metastasizing relatively early to the submandibular triangle and upper jugular chain of lymph nodes. Treatment consists of surgery, often including the removal of the adjacent lymph nodes followed by radiotherapy.

Soft Palate

Squamous cell carcinoma of the soft palate occurs most commonly in its lateral posterior regions adjacent to the anterior faucial pillars. Lesions in this location represent approximately 15% of intraoral carcinoma. Patients commonly are heavy smokers who consume large amounts of alcohol. Lesions are usually erythroplakic or a mixture of red and white plaquelike areas (Figure 6-50). Invasion often occurs before surface ulceration is evident. Most lesions are moderately to poorly differentiated, often invading the deeper structures and metastasizing to the cervical and jugular lymph nodes before large ulcerative or nodular lesions are clinically apparent.

Gingiva and Alveolar Ridge

Lesions of the gingiva and alveolar ridges represent 4% to 6% of intraoral carcinoma and commonly have the initial appearance of a verrucous leukoplakia or an ulceration with rolled borders (Figure 6-51). The mandible is affected more often than the maxilla; most lesions are present in the posterior areas. Lesions are usually well differentiated and invade the underlying bone, often via the periodontal ligament, when teeth are present. Common presenting signs are extensive tooth mobility, early tooth loss in the absence of advanced periodontal disease, and sockets that fail to heal after extraction. In the mandible, metastasis is usually to the submandibular and cervical lymph nodes. Treatment consists of surgical excision; segmental resection may be necessary if bone invasion has occurred.

**FIGURE 6-51**

Squamous cell carcinoma of the gingiva and alveolar ridges.

Buccal Mucosa

The buccal mucosa is infrequently the site of squamous cell carcinoma, accounting for approximately 1% to 2% of intraoral carcinomas. Lesions usually occur as ulcers along the occlusal line (Figure 6-52) and are associated with surrounding induration caused by relatively rapid

**FIGURE 6-52**

Squamous cell carcinoma of the buccal mucosa.

invasion of the deeper structures. Most lesions are moderately differentiated and metastasize to the submandibular lymph nodes. Treatment consists of surgical excision, radiotherapy, or both.

Metastasis

Squamous cell carcinoma of the oral cavity spreads by invading the lymphatic vessels. Once inside these vessels, the tumor cells are carried to the regional lymph nodes where they lodge and continue to proliferate. The proliferating tumor cells expand the involved lymph nodes, eventually penetrate the fibrous capsule of the lymph nodes, and extend into the surrounding tissue. These lymph nodes are clinically detectable by digital palpation and present as firm nodules that are often fixed to the surrounding connective tissues. Enlarged, firm, and fixed lymph nodes are an ominous clinical sign (Figure 6-53).

The lymph nodes that most commonly contain metastatic intraoral squamous cell carcinoma are the submandibular and the superficial and deep cervical nodes. Squamous cell carcinomas of the lower lip that become large enough to metastasize initially involve the submental nodes before spreading to the submandibular and cervical lymph nodes (Figure 6-54). Lesions that spread beyond the regional lymph nodes of the head and neck often metastasize to the lungs and liver.

Clinical Staging of Carcinomas of Head and Neck (TNM System)

Clinical staging of carcinoma is used to designate the extent of malignant disease in a patient and to match it with what has been determined to be the most appropriate treatment for a patient with a comparable

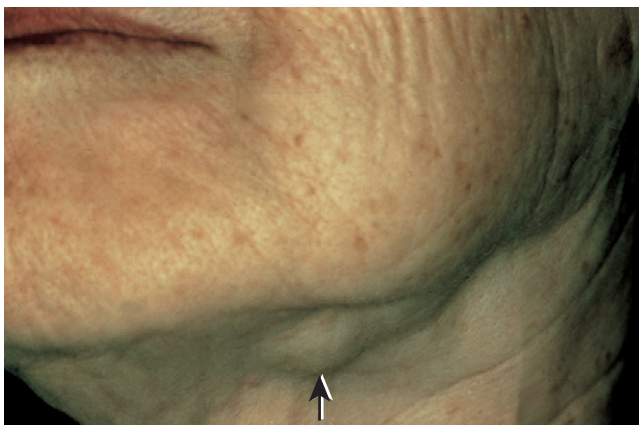


FIGURE 6-53
Enlarged firm fixed submandibular lymph node (arrow) caused by metastasis from an intraoral squamous cell carcinoma.

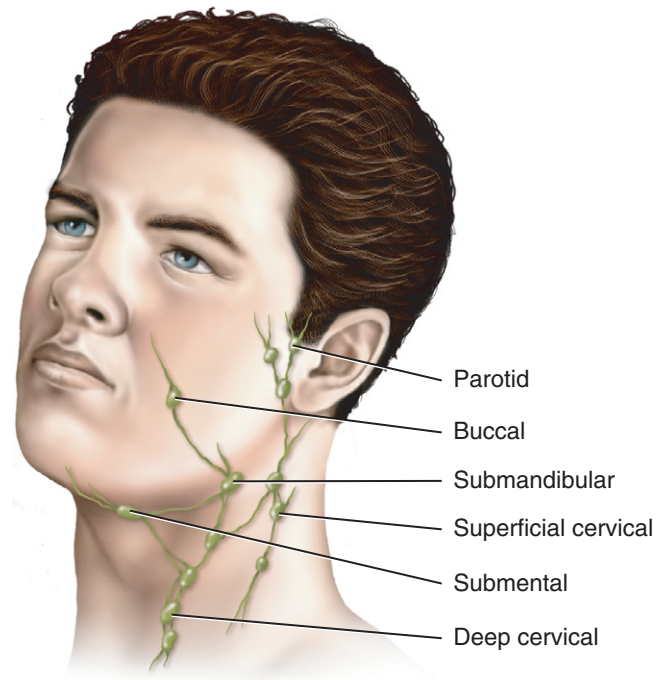


FIGURE 6-54
Lymphatic drainage pathways and major lymph node clusters of the head and neck.

stage. The use of a uniform staging system provides meaningful comparisons of the results of specific types of treatments. The designations used in the TNM system (*T*, primary tumor; *N*, regional lymph node; *M*, distant metastasis) differ somewhat according to the anatomic site. For the oral cavity the TNM definitions and staging groups are outlined in Boxes 6-3 and 6-4.

TREATMENT

Clinicians usually treat squamous cell carcinoma of the oral cavity by surgical excision, radiation therapy, or both. Depending on the size, site, and stage of the lesion, surgical treatment may consist of local excision or a combination of local excision and regional lymph node dissection. For example, squamous cell carcinoma of the vermillion border of the lower lip is usually well differentiated, often diagnosed at an early stage, and can usually be cured by local excision. By contrast, squamous cell carcinomas of the lateral border of the tongue or floor of the mouth are usually not as well differentiated, often diagnosed at later stages, and metastasize sooner. These lesions usually require extensive treatment (usually a combination of surgery, radiation, and possibly chemotherapy) and have a much poorer prognosis.

BOX 6-3**TNM Definitions for Malignant Tumors of the Oral Cavity****T—PRIMARY TUMOR**

- T₀—No evidence of primary tumor
 T_{is}—Carcinoma in situ (CIS)
 T₁—Tumor size, 2 cm or less
 T₂—Tumor size, 2 to 4 cm
 T₃—Tumor size, greater than 4 cm
 T₄—Tumor invades adjacent structures

N—REGIONAL LYMPH NODE

- N₀—No palpable or suspicious node
 N₁—Suspicious, palpable, ipsilateral node
 N₂—Suspicious, palpable, contralateral, or bilateral node
 N₃—Palpable, large, fixed node

M—DISTANT METASTASIS

- M₀—No distant metastasis
 M₁—Clinical or radiographic evidence of metastasis

BOX 6-4**TNM Clinical Staging of Carcinoma of the Oral Cavity**

Stage I	T ₁	N ₀	M ₀			
Stage II	T ₂	N ₀	M ₀			
Stage III	T ₃	N ₀	M ₀			
	T ₁	N ₁	M ₀			
	T ₂	N ₁	M ₀			
Stage IV	T ₃	N ₁	M ₀			
	T ₁	N ₂	M ₀ ;	T ₁	N ₃	M ₀
	T ₂	N ₂	M ₀ ;	T ₂	N ₃	M ₀
	T ₃	N ₂	M ₀ ;	T ₃	N ₃	M ₀
	Any T or N category with M ₁					

Less Common Forms of Squamous Cell Carcinoma

The overwhelming majority of squamous cell carcinomas of the oral cavity are the common generic morphologic type described in the previous section. The remaining oral squamous cell carcinomas consist of several morphologically distinct subtypes. The most common subtypes are verrucous carcinoma, spindle cell carcinoma, and nasopharyngeal carcinoma. On very rare occasions three other subtypes have been identified and will be discussed briefly. They are adenoid squamous cell carcinoma, adenosquamous carcinoma, and basaloid squamous carcinoma.

Verrucous Carcinoma

VERRUCOUS CARCINOMA: A diffuse, largely exophytic, superficial spreading, highly keratinized, warty form of well-differentiated squamous cell carcinoma that is unlikely to metastasize.

Ackerman first recognized verrucous carcinoma as a distinct entity in 1948. Although it also occurs in other anatomic sites, it most commonly occurs in the oral cavity.

CLINICAL FEATURES

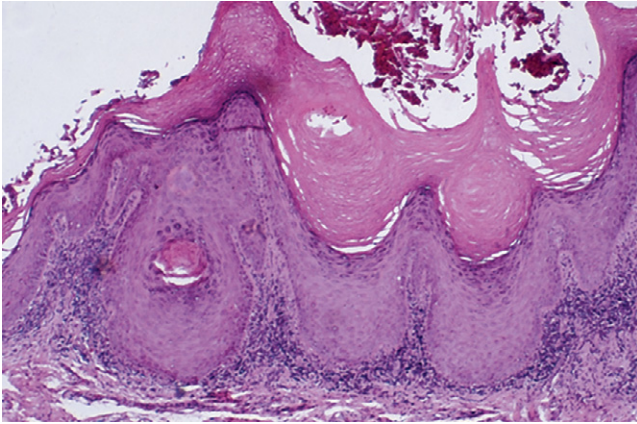
The tumor usually occurs in males and tends to affect individuals over 60 years of age. Most intraoral cases involve the gingiva, alveolar mucosa, and buccal mucosa; however, the hard palate and floor of the mouth can also be involved. The tumor grows slowly, exhibits an exophytic papillary (warty) pattern (Figure 6-55), and tends to be diffusely distributed.

HISTOPATHOLOGY

The surface of the tumor is usually papillary and covered by a thick layer of parakeratin. Deep crypts containing plugs of parakeratin usually occur between the elongated surface projections. The epithelium is dysplastic but seldom exhibits severe dysplastic features. The basement membrane remains intact, and an intense chronic inflammatory cell infiltrate is often present in the underlying connective tissue. The interface between the tumor and the adjacent normal epithelium is usually well defined with minimal if any penetration of epithelial cells along a broad, blunt leading margin of the bulb-shaped rete ridges (Figure 6-56). Compression of underlying superficial muscle bundles and superficial resorption (saucerization) of cortical bone is sometimes observed in long-standing lesions.

**FIGURE 6-55**

Verrucous carcinoma. Lesions commonly are diffuse, white, exophytic, and papillary.

**FIGURE 6-56**

Verrucous carcinoma. The microscopic features exhibit extensive keratin production, forming fingerlike projections and filling deep crypts; acanthosis with broad blunt bulbous rete ridges compressing the underlying connective tissue; absent or minimal dysplasia; and an intact basement membrane.

TREATMENT

Because of its superficial and cohesive growth pattern and sharply demarcated margins, verrucous carcinoma is ideally suited to treatment by either surgical excision or laser therapy. The prognosis is good, because local excision is usually curative. New lesions in adjacent sites may occur.

Spindle Cell Carcinoma

SPINDLE CELL CARCINOMA: *An uncommon form of poorly differentiated squamous cell carcinoma characterized by spindle-shaped tumor cells that resemble a fibrosarcoma.*

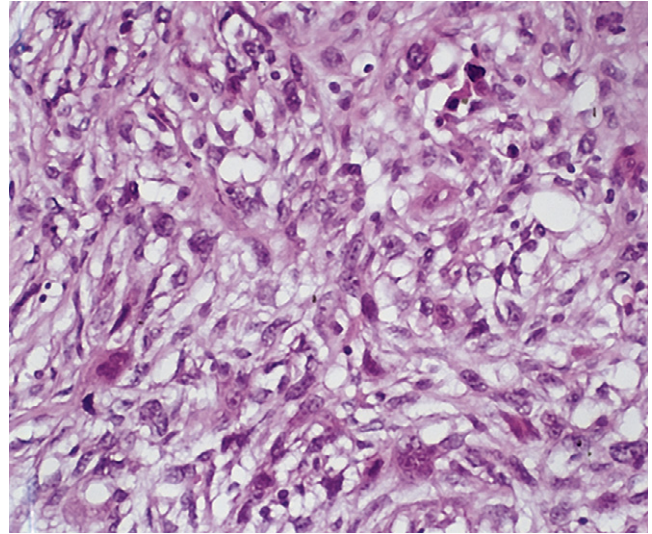
Spindle cell carcinoma is an uncommon variant of squamous cell carcinoma in which the epithelial cells lose their cohesive character and polygonal shape and resemble malignant fibroblasts (spindle cells). These lesions can be mistaken for fibrosarcoma.

CLINICAL FEATURES

Spindle cell carcinoma occurs primarily in males and most often affects the lower lip and tongue. Occasionally, the alveolar mucosa or gingiva is involved. This subtype of squamous cell carcinoma is often less aggressive than other forms of poorly differentiated carcinoma.

HISTOPATHOLOGY

The lesion is usually ulcerated with malignant cells streaming from the tips of tapered and elongated epithelial rete pegs adjacent to the ulcerated zone. Curiously, the other layers of the epithelium exhibit a minimal degree of dysplasia. In some lesions, in addition to the spindle cell component, areas of recognizable squa-

**FIGURE 6-57**

Spindle cell carcinoma. The microscopic features demonstrate a poorly differentiated lesion containing randomly oriented spindled epithelial cells resembling fibroblasts. The cells exhibit pleomorphism, hyperchromatism, and a lack of keratin production.

mous cell carcinoma with foci of keratin formation are sometimes observed. An inflammatory cell infiltrate consisting of lymphocytes and neutrophils or eosinophils is often present. Despite its apparent lack of differentiation, spindle cell carcinoma usually exhibits few mitotic features (Figure 6-57).

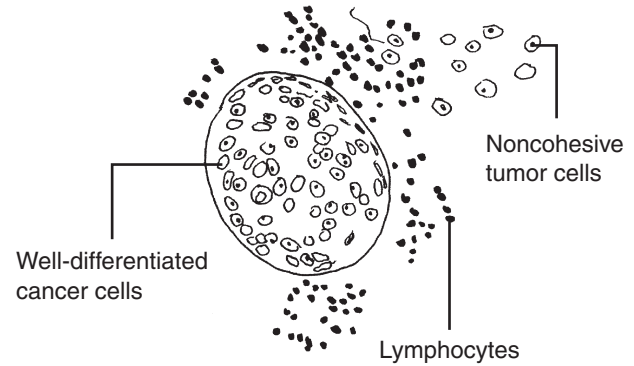
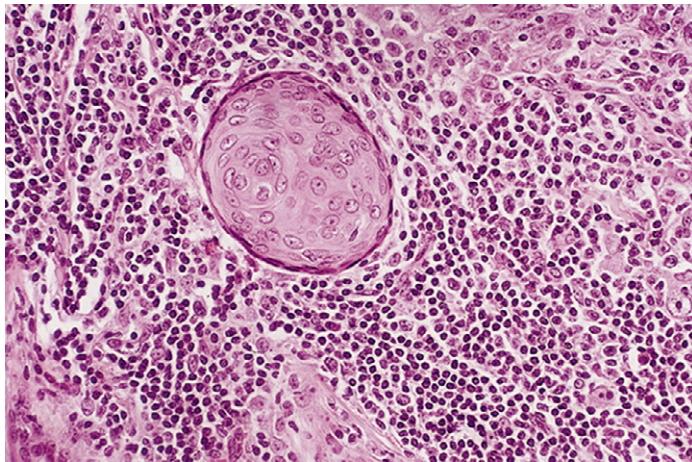
TREATMENT

Spindle cell carcinoma metastasizes and needs to be treated aggressively. Surgical excision appears to be the most effective mode of treatment.

Nasopharyngeal Carcinoma

NASOPHARYNGEAL CARCINOMA: *An aggressive form of squamous cell carcinoma located in the nasopharynx and having varying degrees of differentiation; often first discovered as a metastatic lesion in a lateral neck lymph node.*

Of the anatomic locations immediately adjacent to the oral cavity, the nasopharynx is most commonly afflicted with squamous cell carcinoma. The lesions in this site are usually less differentiated than those found in the oral cavity. In 1978 the WHO proposed that the various forms of squamous cell carcinoma found in the nasopharynx be divided into three categories based on their degree of histologic differentiation. The categories proposed were (1) **keratinizing carcinoma**, (2) **nonkeratinizing carcinoma**, and (3) **undifferentiated carcinoma**. This has

**FIGURE 6-58**

Nasopharyngeal carcinoma (keratinizing type). Microscopic features of the lesion exhibit a central island of well-differentiated squamous cell carcinoma.

been widely accepted and useful in standardizing the histology and treatment of lesions in this anatomic location.

Patients with nasopharyngeal carcinoma do not fit the usual profile of those with oral squamous cell carcinoma; consequently, a different causative factor has long been suspected. Although some evidence suggests an association with EBV in the nonkeratinizing and undifferentiated types, the evidence is weaker for an association between the virus and the keratinizing type. No strong direct evidence has been established that supports a causal relationship between EBV and nasopharyngeal carcinoma.

CLINICAL FEATURES

In the United States, nasopharyngeal carcinoma accounts for 0.25% of all cancers and occurs in all age groups but more commonly in males by a 3:1 ratio. For unknown reasons, nasopharyngeal carcinoma is one of the more common forms of cancer in China and accounts for 18% of all human malignancies. It is particularly prevalent in China's southern and northern provinces and on the island of Taiwan. Nasopharyngeal carcinoma is usually found during an investigation of an asymptomatic lateral neck mass, because the lymph nodes of the lateral neck are the usual sites of initial metastases. Other presentations are nasal obstruction, unilateral otitis media, epistaxis, and otalgia.

HISTOPATHOLOGY

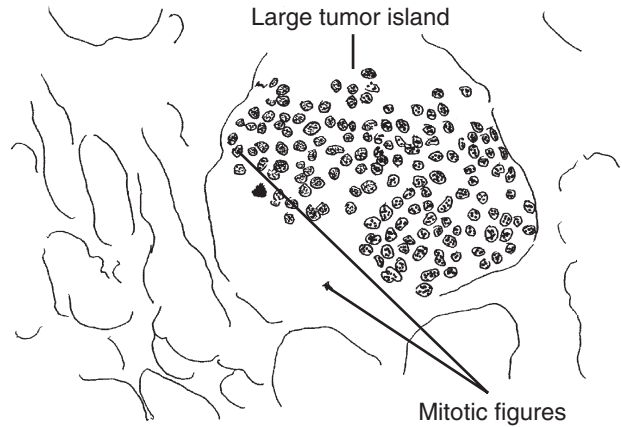
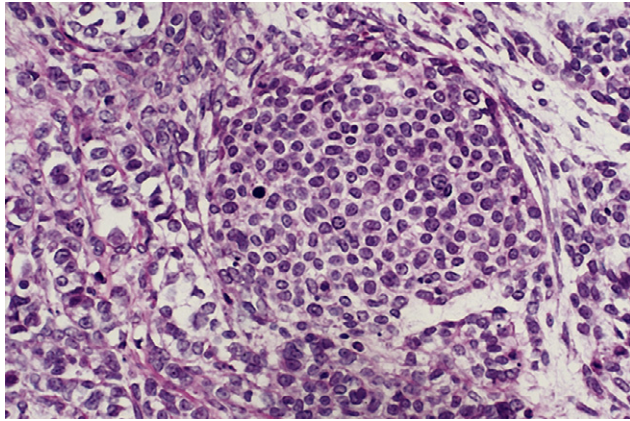
Keratinizing carcinoma of the nasopharynx represents 25% of nasopharyngeal carcinomas and exhibits all the features of the usual well-differentiated or moderately differentiated squamous cell carcinoma found elsewhere in the oropharynx. Microscopic examination reveals distinct intercellular bridges (desmosomes), intra-

cellular keratin production, and keratin pearl formation within islands of epithelial cells (Figure 6-58).

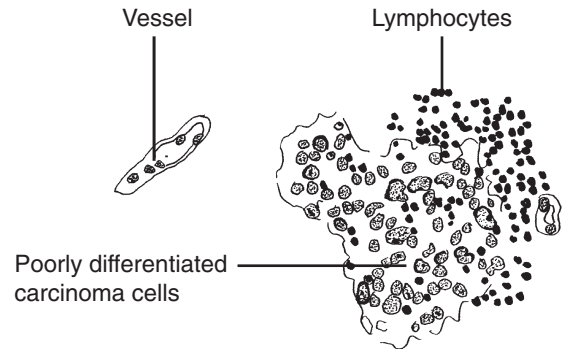
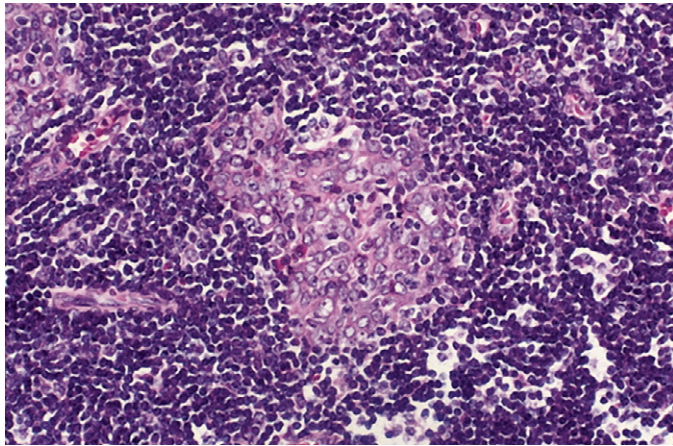
Nonkeratinizing carcinoma also constitutes 25% of nasopharyngeal carcinomas. It exhibits the clumping features characteristic of squamous epithelium; individual cells exhibit distinct cytoplasm and visible desmosomes, but little or no evidence of keratin production exists (Figure 6-59). These cell clumps are like those of the transitional cell carcinoma of the urinary bladder. In the past, lesions with this histologic pattern were termed *transitional cell carcinoma*. Undifferentiated carcinoma is the most common form, representing 50% of these carcinomas. It differs from other carcinomas by having neoplastic cells that are often difficult to recognize as being of epithelial origin. The cells have scant and indistinct cytoplasm surrounding a rounded vesicular nucleus with large prominent nucleoli. The cells may be in a syncytial arrangement rather than in the sheets that are common to squamous cell neoplasms. They are also distinguished by the presence of large aggregates of nonneoplastic lymphocytes surrounding the epithelial component (Figure 6-60). Because of the intermingling of the two types of tissues, this form of the nasopharyngeal carcinoma was previously designated as *lymphoepithelioma*. It is not uncommon for an individual lesion to have more than one of the three aforementioned histologic patterns.

TREATMENT

Because of the generally inaccessible anatomic location of a carcinoma in the nasopharynx, the immediate adjacency of vital structures, and the radiosensitivity of the two nonkeratinizing lesions, surgical treatment is usually not undertaken. The keratinizing type of carcinoma is not very radioresponsive; thus the 5-year survival rate of patients with these lesions is only 10% to

**FIGURE 6-59**

Nasopharyngeal carcinoma (nonkeratinizing type). Microscopic features of the lesion demonstrate sheets of randomly oriented poorly differentiated epithelial cells with no keratin production evident.

**FIGURE 6-60**

Nasopharyngeal carcinoma (undifferentiated type). Microscopic features of the lesion exhibit small islands and individual cells that are poorly differentiated against a background of densely packed normal lymphocytes.

20%. Patients with nonkeratinizing lesions have variable responses to radiotherapy and have a 5-year survival rate of 35% to 50%. The undifferentiated lesions are most responsive to radiation and have a 5-year survival rate of 60%.

Adenoid Squamous Cell Carcinoma

ADENOID SQUAMOUS CELL CARCINOMA: An uncommon type of low-grade epithelial malignancy of the sun-exposed skin of the face and lower lip.

The adenoid squamous cell carcinoma is a well-differentiated neoplasm that occurs primarily on the face, including the vermilion border of the lower lip. It does not occur within the oral cavity. This tumor is re-

ferred to by a number of names, including *adenoacanthoma*, *acantholytic squamous cell carcinoma*, and *pseudoglandular squamous cell carcinoma*.

CLINICAL FEATURES

Lesions arise on sun-damaged skin, specifically in areas of actinic (solar) keratosis of the acantholytic type.

HISTOPATHOLOGY

The tumor tends to be well circumscribed at its lateral and deep margins and resembles the profile of KA. The peripheral cells of the tumor exhibit the features of a well-differentiated squamous cell carcinoma and one or more irregular, slitlike, or cystic areas containing acantholytic and dysplastic cells.

Surgical excision of an adenoid squamous cell carcinoma is the treatment of choice and is usually curative. If the tumor is incompletely excised, it can recur locally; however, metastasis is rare.

Adenosquamous Carcinoma

ADENOSQUAMOUS CARCINOMA: *Rare, aggressive carcinoma of the mucosa consisting of a mixture of malignant squamous and glandular cells.*

CLINICAL FEATURES

Adenosquamous carcinoma is a rare, aggressive carcinoma that occurs within the oral and nasal cavities and in the larynx. Within the oral cavity, it occurs primarily on the floor of the mouth and the hard palate.

HISTOPATHOLOGY

Adenosquamous carcinoma appears to be simultaneously derived from the surface mucosa and the adjacent minor salivary gland ducts. The histologic appearance resembles a high-grade mucoepidermoid carcinoma.

TREATMENT

The tumor has a marked tendency to metastasize to regional lymph nodes and distant sites. Because of its metastatic potential, the tumor has a poor prognosis.

Basaloid Squamous Cell Carcinoma

BASALOID SQUAMOUS CELL CARCINOMA: *Rare, aggressive form of poorly differentiated squamous cell carcinoma consisting of medullary patterns of cells with central areas of necrosis.*

The basaloid squamous cell carcinoma (BSCC) is a relatively new entity (first described in 1986). Before it was defined as a separate entity, the BSCC was often diagnosed as an adenoid cystic carcinoma or an adenoid type of basal cell carcinoma.

CLINICAL FEATURES

It is an aggressive malignancy that occurs primarily at the base of the tongue, larynx, piriform sinus, and tonsil. Males are affected far more often than females; the gender ratio is approximately 7:1. Most of the reported cases have been in habitual smokers, many of whom also consumed significant amounts of alcohol. The average age of the patients affected by this tumor is approximately 60 years.

HISTOPATHOLOGY

Lesions are composed of closely packed, moderately pleomorphic, basaloid cells that form variable-sized islands and cords. The larger islands of tumor cells often exhibit a central focus of comedo-type (doughnutlike) necrosis.

The smaller islands of tumor cells often exhibit prominent individual cell necrosis (apoptosis). Cells at the periphery of the tumor islands tend to exhibit nuclear palisading. A cribriform growth pattern similar to that seen in adenoid cystic carcinoma is frequently present. Many cases exhibit a zone of stromal hyalinization around the neoplastic islands. Mitotic figures, including atypical forms, are often numerous. Foci of squamous differentiation are always present. This most commonly consists of cells with abundant eosinophilic cytoplasm or collections of keratinized cells within the basaloid cell islands. Keratin pearl formation may or may not be present. The junction between the squamous cells and the adjacent basaloid tumor cells is usually abrupt, with little or no transition. In most cases the overlying surface epithelium exhibits severe dysplasia or CIS, which is in continuity with the BSCC.

TREATMENT

At the time of initial diagnosis, the majority of patients with BSCC exhibit metastases to regional lymph nodes or distant metastases (stage III or IV diseases). Like the adenosquamous carcinoma, BSCC tends to metastasize widely and has a poor prognosis.

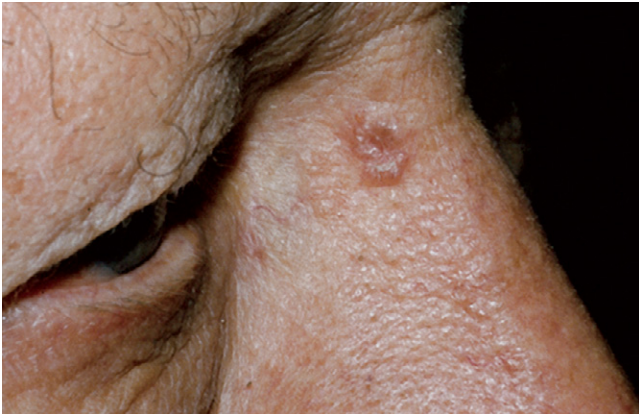
Basal Cell Carcinoma

BASAL CELL CARCINOMA: *Common, locally destructive, nonmetastasizing malignancy of the skin; composed of medullary patterns of basaloid cells.*

Basal cell carcinoma is a malignant tumor of hair-bearing areas of the skin. It does not arise on mucous membranes; however, it can involve mucous membranes by directly spreading from adjacent skin. The majority of basal cell carcinomas arise on the sun-exposed skin of the upper part of the face, including the forehead and ears, in individuals with fair skin. Individuals with dark skin are rarely affected. Chronic occupational or recreational exposure to direct sunlight (actinic radiation) is a known cause of this tumor. Males are more commonly affected than females. The incidence of basal cell carcinoma is particularly high in regions with high temperatures and low humidity. Notable examples are Queensland in Australia and Arizona in the United States. Basal cell carcinoma can develop in the fourth decade of life, but it usually develops in older patients. An exception is seen in individuals with the nevoid basal cell carcinoma syndrome (Gorlin-Goltz syndrome), in which the tumors develop in the second and third decades of life.

CLINICAL FEATURES

The basal cell carcinoma usually starts as a slightly elevated papule that slowly enlarges and eventually develops a central, crusted ulcer with an elevated smooth-rolled border (Figure 6-61). If untreated, the tumor enlarges and invades adjacent tissues and structures by

**FIGURE 6-61**

Basal cell carcinoma. Early incipient lesion on the bridge of the nose that exhibits the raised smooth borders with the depressed center.

**FIGURE 6-62**

Basal cell carcinoma. Advanced lesion with characteristic irregular shape and central nonhealing ulcer. An adjacent satellite lesion is present.

direct extension (Figure 6-62) but rarely metastasizes. Although most basal cell carcinomas are solitary tumors, those occurring in the Gorlin-Goltz syndrome are often multiple.

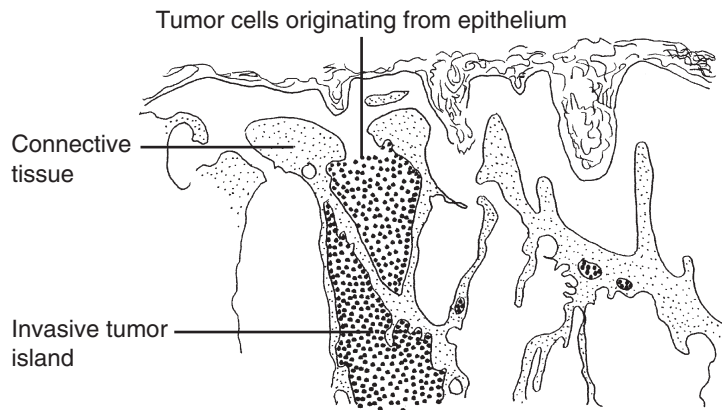
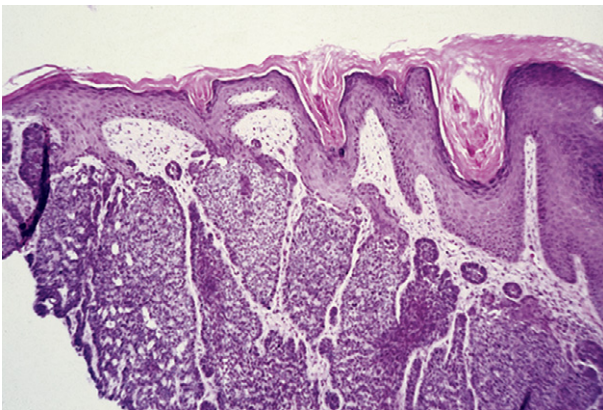
HISTOPATHOLOGY

The basal cell carcinoma is characterized by a proliferation of basaloid epithelial cells (Figure 6-63) exhibiting a spectrum of growth patterns ranging from solid (Figure 6-64, A) to adenoid or cystic (Figure 6-64, B). The cells at the periphery of the tumor islands are usually palisaded and hyperchromatic. The central cells may be polyhedral, oval, round, or spindle shaped. Intercellular bridges are seldom seen in routine tissue sections. Mitotic figures can vary from few to numerous. Apoptosis (individual cell death) of tumor cells is commonly seen.

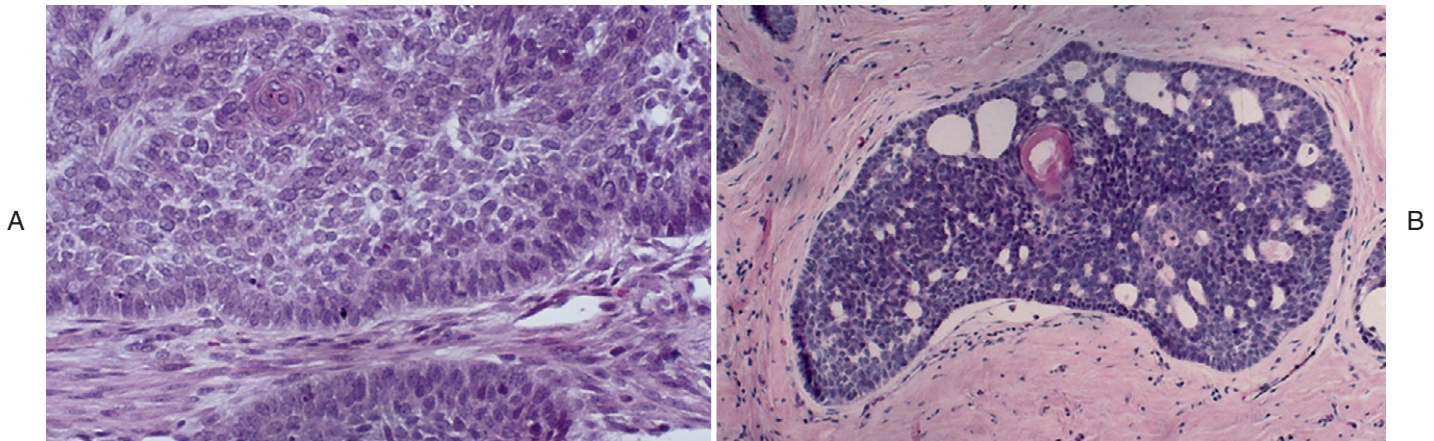
The fibrous stroma around the tumor islands is variably cellular and often exhibits large amounts of acid mucopolysaccharides. During tissue processing, dehydration causes the mucopolysaccharides to shrink, resulting in the formation of retraction spaces (clefts) that separate the stroma from the tumor islands. This is a common but not a constant histologic artifact seen in tissue sections of basal cell carcinoma. Another frequently seen feature in the stroma of basal cell carcinoma is an increase in the elastic tissue content and focal deposits of amyloid.

TREATMENT

Basal cell carcinoma can be treated by a number of modalities. The most common are excisional surgery, radiation, and electrocautery. In an individual case the

**FIGURE 6-63**

Basal cell carcinoma. Microscopic features of raised margin illustrate a proliferation of cells from the basal cell layer and extension of the tumor cells laterally beneath the overlying normal skin.

**FIGURE 6-64**

Basal cell carcinoma. **A**, High-power microscopy of islands of basal cell carcinoma with a peripheral layer of palisaded cells and a central area composed of uniform basal and parabasal cells. **B**, Medium-power microscopy of an island of basal cell carcinoma exhibiting the less common microcystic (adenoid) pattern. Included is a focal area of keratinization.

modality of treatment is dictated by a variety of factors. The most common are size and site of the lesion and the age of the patient. Although basal cell carcinoma has a distinct tendency to recur after conservative treatment, the cure rate using the previously mentioned modalities is approximately 95%.

MELANOMA

MELANOMA: *Malignant neoplasm of melanocytes occurring on skin and mucosal surfaces; commonly has a radial and superficial initial growth period before it extends into the deeper underlying tissues and metastasizes.*

Melanoma, also termed *malignant melanoma*, most commonly occurs on the skin, where it is divided into four main types: (1) superficial spreading, (2) lentigo maligna, (3) acral lentiginous, and (4) nodular.

Melanomas also occur on the mucous membranes, including the oral mucosa. On the skin, melanomas tend to develop on the sun-exposed areas in fair-skinned individuals who have had prolonged exposure to strong direct sunlight. Recent data from Scandinavia, Australia, and the United States indicate that the incidence of cutaneous melanoma is increasing, having tripled in the last 40 years. Although the median age of patients with the initial diagnosis of skin lesions is 53, it is the most common malignancy of young, white adults, occurring more commonly in males than in females. Sunshine (actinic radiation) is the only factor that is strongly implicated in the cause of skin melanoma. Because melanoma also occurs on surfaces not exposed to the sun, other unknown factors most likely exist.

Oral melanoma is considered rare when compared with the incidence of skin melanoma. Oral melanoma, like skin melanoma, occurs in individuals who are in the 40- to 60-year age group. Most cases of oral melanoma arise on the hard palate and maxillary gingiva.

SKIN AND MUCOSAL MELANOMA

Melanoma of both skin and mucosal tissues have similar basic features. They can be dark brown, bluish-black, or black. On rare occasions, a nonpigmented melanoma (*amelanotic melanoma*) is found that is reddish rather than brown or black. Most lesions have an early macular pattern and become papular, nodular, or both in later stages. A nodular melanoma occurs that does not have a significant macular stage.

Most melanomas, including those within the oral cavity, tend to grow in two phases: (1) an initial radial-growth phase followed by (2) a vertical-growth phase. During the radial-growth phase the neoplastic cells spread laterally in all directions but remain confined to the surface epithelium. The vertical-growth phase begins when the neoplastic cells invade and populate the connective tissue. The duration of the radial-growth phase can differ significantly among different types of melanoma.

SUPERFICIAL SPREADING MELANOMA

SUPERFICIAL SPREADING MELANOMA: *Most common form of malignant melanoma, initially appearing as an irregularly shaped brown-black macular area with jagged borders and satellite lesions in which areas of nodular melanoma eventually develop.*

CLINICAL FEATURES

Superficial spreading melanoma is the most common type of melanoma on skin and mucous membranes, accounting for approximately 80% of all lesions. Superficial spreading melanoma is most commonly found in middle-age patients. The radial-growth phase consists of a tan, brown, or black variegated macule or plaque

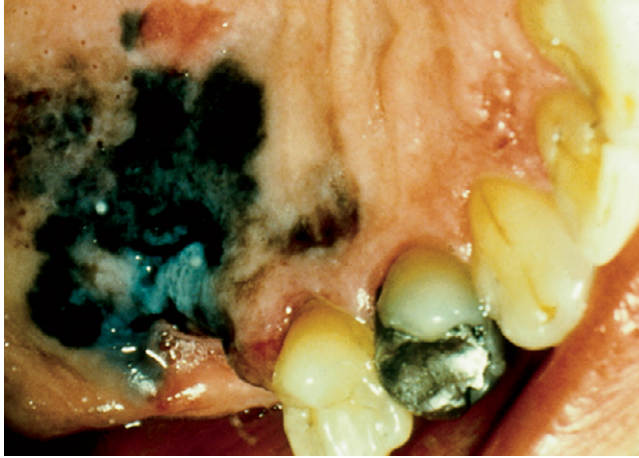


FIGURE 6-65

Superficial spreading melanoma. The lesion is brown-black with irregular margins and multiple satellite lesions. The location on the anterior palate is common. (Courtesy Dr. A.M. Rees.)

that exhibits an irregular outline (Figure 6-65). Frequently, one or more nearby satellite lesions are present. The radial-growth phase may last from several months to several years. During this phase the lesion becomes larger, more intensely pigmented, and eventually nodular and ulcerated.

HISTOPATHOLOGY

The radial-growth phase is characterized by the presence of large atypical melanocytes within the epithelial layer that exhibit abundant pale cytoplasm and are arranged in small round clusters at the epithelial connective tissue interface (Figure 6-66). Focal microinvasion is usually evident. The term *pagetoid* is usually used to describe the clear cells in the unique intraepithelial growth pattern in superficial spreading melanoma. The nodular and ulceration stage is characterized by frank invasion of the connective tissue by tumor cells, which are usually arranged in an alveolar pattern. The individual tumor cell exhibits abundant pale cytoplasm containing variable amounts of fine, powdery melanin that imparts a dusty appearance to the cytoplasm. Mitotic figures may or may not be conspicuous. Significant pseudoepitheliomatous hyperplasia of the overlying epithelium may accompany the invading tumor cells. The diagnosis of melanoma can be confirmed with positive immunohistochemical stains for S-100, HMB-45, Melan-A, and vimentin.

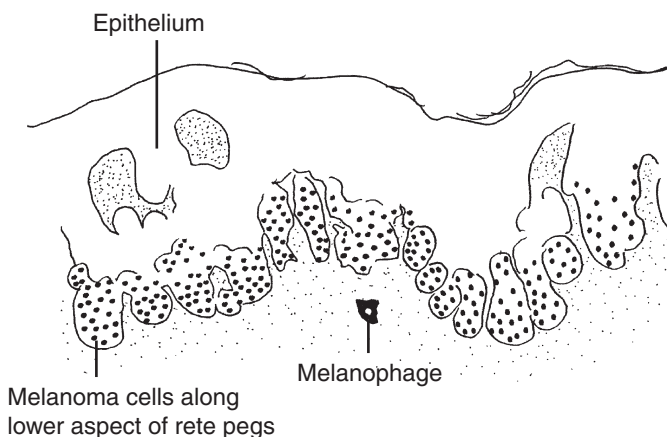
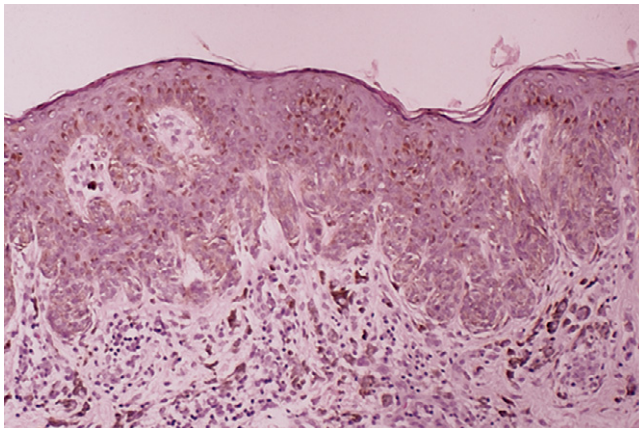


FIGURE 6-66

Superficial spreading melanoma. Microscopic features of a lesion before the vertical-growth stage (invasion) reveal the proliferation of abnormal melanocytes within the basal cell layer, producing a nodular pattern of the tips of the rete pegs. The dark coloration of most lesions is due to the greatly increased numbers of atypical melanocytes and the resulting excess melanin production. The melanin is usually contained within melanophages located in both the upper layers of the epithelium and underlying connective tissue.

LENTIGO MALIGNA MELANOMA

LENTIGO MALIGNA MELANOMA: *Slowly evolving melanoma that develops within a preexisting pigmented macular lesion on the sun-exposed skin of older patients.*

CLINICAL FEATURES

Lentigo maligna melanoma occurs only on sun-exposed areas of the skin, primarily on the cheeks and temples of older white men and women. It is an uncommon form of melanoma, representing 5% of lesions. It usually arises in a preexisting pigmented lesion known as *Hutchinson melanotic freckle* and evolves slowly over a period of 15 or more years. The lentigo maligna presents as a relatively large, irregular and asymmetric, variegated macular lesion. The color varies extensively from light tan to black, the latter usually indicative of malignancy. Some lesions exhibit a central area of pale scarring, a sign that some regression has occurred.

HISTOPATHOLOGY

In lentigo maligna melanoma the epithelium is atrophic; the basal layer exhibits increased numbers of cytologically atypical melanocytes with variable amounts of coarse melanin granules. Although in most instances the atypical melanocytes are singularly scattered throughout the basal layer, some small nests of cells may also be present. Intraepithelial spreading of tumor cells may be present. As the lesion progresses, the intensity of the pigmentation increases and individual atypical melanocytes begin appearing in the superficial connective tissue. This early invasive or vertical-growth phase is usually accompanied by a fibroblastic and lymphohistiocytic host response. During the advanced invasive phase the neoplastic melanocytes are often spindle shaped and may exhibit desmoplasia or neurotropism.

ACRAL LENTIGINOUS MELANOMA

ACRAL LENTIGINOUS MELANOMA: *Brown, irregularly shaped macular lesion of the skin of the palms of the hands and soles of the feet that undergoes progression to nodular melanoma.*

Acral lentiginous melanoma occurs primarily on the palms of the hands, soles of the feet, and nail beds (especially the thumb and great toe). It has a mucosal counterpart, termed *mucosal lentiginous melanoma*, which is found on the mucocutaneous junction and the oral mucous membranes. In the mouth the diagnosis of mucosal lentiginous melanoma is seldom made, because in this location it is essentially indistinguishable from superficially spreading melanoma.

CLINICAL FEATURES

Acral lentiginous melanomas of the skin occur in all races and appear to be unrelated to extent of exposure to sunlight. They represent 8% of all melanomas. This type of melanoma starts as a brown variegated macule with irregular borders. As the tumor enlarges it becomes ulcerated, papular, or nodular, which is indicative of its transition from a superficial spreading (radial) growth phase to an invasive (vertical) growth phase.

HISTOPATHOLOGY

The macular phase of skin lesions exhibits a basilar proliferation of individual large atypical melanocytes that impart a vacuolated appearance to the basal region of the epithelium. Mitotic figures may or may not be seen during the radial-growth phase. The basal arrangement of the palisaded melanoma cells constitutes the lentiginous pattern. As the tumor assumes a papular and nodular appearance, confluent masses of neoplastic melanocytes, which are frequently spindle shaped, extend into the connective tissue. Many of these lesions exhibit a marked infiltrate of lymphocytes that may assume a lichenoid pattern at the epithelial and mesenchymal junction. In these cases a lymphocytic infiltrate can obscure the presence of the neoplastic melanocytes. Detailed microscopic examination supplemented with immunohistochemical staining is required in these cases.

NODULAR MELANOMA

NODULAR MELANOMA: *A form of melanoma of the skin and occasionally the mucosa that arises as a raised mass with a limited macular radial-growth phase, quickly invades and metastasizes, and consists of a wide variety of cell shapes and sizes.*

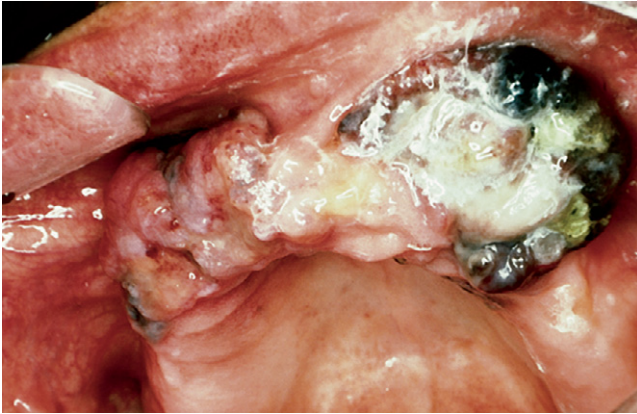
Nodular melanoma is the second most common form of melanomas, accounting for 15% of these lesions. It primarily occurs on skin but is also found on oral mucous membranes. It differs significantly from the other types by having little or no radial-growth phase but exhibiting a prominent vertical-growth phase almost from its inception. Occasionally, lesions do not contain clinically or even microscopically detectable melanin-induced pigmentation.

CLINICAL FEATURES

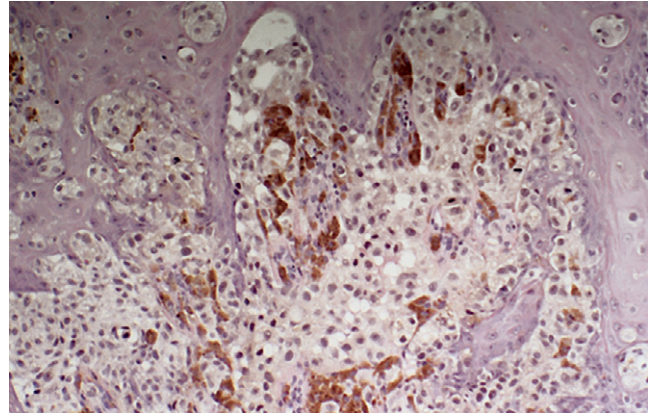
The lesion consists of combinations of pink, red, brown, and black nodules, many of which are ulcerated (Figure 6-67). Evidence of metastasis is found early in the disease process.

HISTOPATHOLOGY

In most cases, by the time a tissue sample is secured, the connective tissue is usually densely packed with tumor cells. The cells exhibit a variety of morphology

**FIGURE 6-67**

Nodular melanoma. The lesion is large with a nodular surface containing ulceration and areas of dark and partial pigmentation intermingled with nonpigmented areas.

**FIGURE 6-68**

Nodular melanoma. Microscopic features reveal a variety of cell types. The most common is a large epithelioid cell with either a clear or pink cytoplasm. Other cells are spindled and some are small, round, and dense, resembling lymphocytes. Melanin deposits are sporadically distributed.

types, the most common being epithelioid with lightly pink or clear cytoplasm; others are spindle-shaped and lymphocyte-like (Figure 6-68). Different parts of the tumor may have different mixtures of the cell types. Normal and abnormal mitotic figures and pleomorphic cells are frequent. Melanin deposition is usually sporadic, with large areas devoid of such deposits. In other areas heavy deposits of melanin granules are commonly present and usually obscure the features of the individual cells. The surface epithelium at the margins of the tumor is usually free of the malignant cells, indicating the absence of a radial-growth phase.

TREATMENT

The key to the treatment of melanoma is early diagnosis while it is still in its radial-growth phase, followed by prompt surgical excision of the lesion. During the radial-growth phase, melanomas are thin (most of the tumor cells are located in or immediately adjacent to the epithelium) and can therefore be excised with relative ease. When measuring the thickness of melanoma, it has been shown that melanomas that are less than 0.76 mm thick rarely metastasize; most are curable. Such tumor thickness is determined during microscopic evaluation by the pathologist, who uses a micrometer to measure from the top of the granular layer of the epithelium to the level of the deepest tumor cell.

In addition to tumor thickness, the rate of mitotic activity within the vertically growing neoplastic cells has also proven to be a valuable prognostic indicator for melanoma. Other factors that have some effect on the prognosis of melanoma include gender of the patient, anatomic site of the lesion, and the presence or absence of tumor-infiltrating lymphocytes.

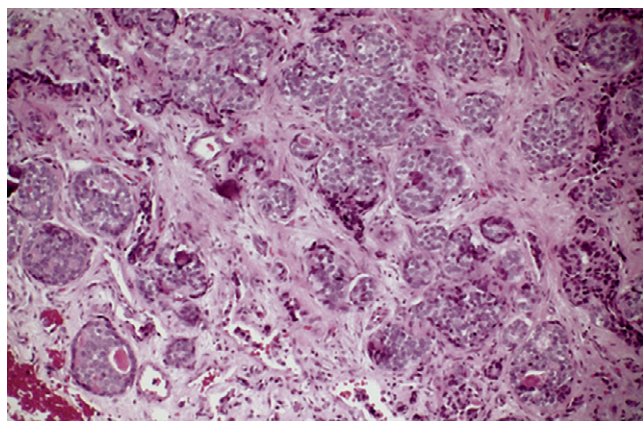
Because of its prominent vertical-growth pattern, nodular melanoma tends to invade deeply and metastasize early. Melanomas that have metastasized to regional lymph nodes or distant sites have a relatively poor prognosis. Chemotherapy and immunotherapy for metastatic melanomas are presently at the experimental and clinical stages of development. Regardless of treatment, nodular melanoma that has entered the vertical-growth phase exhibits a relatively poor prognosis.

METASTASES TO THE JAWS

Metastasis to the oral region from a malignant tumor elsewhere in the body is an uncommon but clinically important finding, because it may be the first indication that the patient has a distant primary tumor. The vast majority of metastases from distant primary lesions to the oral region occur in the mandible, although the maxilla can also be affected. Although metastatic lesions within the mandible can be asymptomatic, most patients experience some degree of discomfort or pain, which is often followed by loosening of teeth or unilateral paresthesia or anesthesia of the lower lip or chin. The development of these symptoms should alert the clinician to the potential presence of metastatic disease. Some degree of swelling or expansion of the mandible, primarily in the molar region, is also often present. The pathway for the metastatic spread of tumor cells to the mandible from a distant primary, such as the kidney, has usually been ascribed to the paravertebral plexus of veins (Batson plexus).

**FIGURE 6-69**

Metastatic adenocarcinoma from breast. The radiograph reveals a large mixed radiolucent and radiopaque area in the posterior mandible.

**FIGURE 6-70**

Metastasis to the jaws. The microscopic features of soft tissue removed from within the mandible suggest a metastatic lesion, because the cells are in small clusters separated by relatively normal connective tissue. Some cell nests contain pools of eosinophilic coagulum that suggests the lesion is an adenocarcinoma.

The radiographic appearance of the mandible at the site of a metastatic tumor deposit can range from an ill-defined radiolucency to an ill-defined radiopacity, or it may appear as a mixed radiolucent and radiopaque lesion (Figure 6-69). The microscopic appearance usually suggests that a lesion is metastatic, because the cells will often be present in clusters of various sizes that are separated by normal resident tissue or fibrous connective tissue replacement (Figure 6-70).

The majority of tumors that metastasize to the jaw are adenocarcinomas. The site of origin of the most common primary tumors and the approximate relative frequency of metastasis to the jaws are as follows: breast

Table 6-3 Incidence of Metastasis of Systemic Malignancies to the Jaws

Origin	Approximate Relative Frequency of Metastasis to the Jaws
Breast	30%
Lungs	20%
Kidney	15%
Thyroid	5%
Prostate	5%
Colon	5%
Stomach	5%
Skin melanoma	5%

(30%), lung (20%), kidney (15%), thyroid (5%), prostate (5%), colon (5%), stomach (5%), and cutaneous melanoma (5%) (Table 6-3).

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7 Oral Infections

CHAPTER OUTLINE

VIRAL INFECTIONS

Herpes Viruses
 Herpes Simplex Virus
 Varicella-Zoster Virus
 Epstein-Barr Virus
 Cytomegalovirus
 Human Herpesvirus 6, 7, and 8
 Coxsackie Viruses
 Herpangina
 Hand, Foot, and Mouth Disease
 Acute Lymphonodular Pharyngitis
 Togavirus
 Rubella
 Paramyxoviruses
 Measles
 Mumps (Epidemic Parotitis)
 Human Papilloma Viruses
 Squamous Papilloma
 Verruca Vulgaris
 Condyloma Acuminatum
 Focal Epithelial Hyperplasia
 Retroviruses
 Human Immunodeficiency Virus

BACTERIAL INFECTIONS

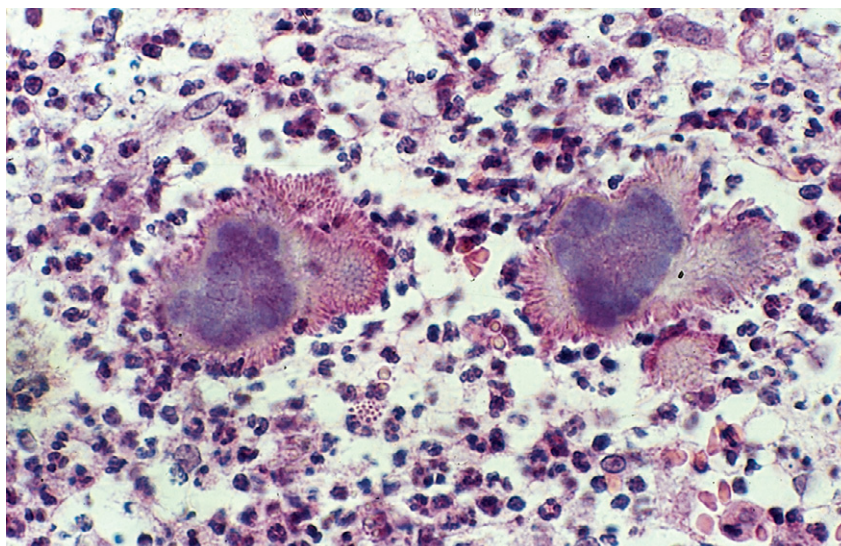
Streptococcus
 Pharyngitis and Tonsillitis
 Scarlet Fever
 Impetigo
Staphylococcus
 Osteomyelitis
Mycobacterium
 Tuberculosis
Treponema Pallidum
 Syphilis
Actinomyces
 Oral-Cervicofacial Actinomycosis

MYCOSES

Candida Albicans
 Acute Pseudomembranous Candidiasis (Thrush)
 Atrophic (Erythematous) Candidiasis
 Chronic Hyperplastic Candidiasis
 Angular Cheilitis (Perlèche)
 Median Rhomboid Glossitis
 Chronic Mucocutaneous Candidiasis
Histoplasma Capsulatum
 Histoplasmosis
Coccidioides Immitis
 Coccidioidomycosis
Cryptococcus Neoformans
 Cryptococcosis
Blastomyces Dermatitidis
 North American Blastomycosis
Aspergillus
 Aspergillosis
 Zygomycota *Mucor* and *Rhizopus*
 Rhinocerebral Zygomycosis

ADDITIONAL KEY TERMS

Candidal leukoplakia
 Chicken pox
 Fungus ball
 Hutchinson triad
 Infectious mononucleosis
 Reverse transcriptase
 Shingles
 Strep throat
 Sulfur granules



VIRAL INFECTIONS

Viruses are among the simplest and smallest microorganisms that infect humans. They consist of a single or double strand of DNA or RNA surrounded by a protein coat termed a *capsid*. These two structures constitute the nucleocapsid, or core, of the virus. The core virion is the viral component responsible for infection. Because a virion lacks the necessary cytoplasmic constituents of higher life forms, it is unable to perform metabolic or protein synthesis functions. A virus is an obligate parasite, because it must enter a host cell of a higher life form to replicate and undertake macromolecular synthesis. Viruses are not able to enter all of the cells they encounter; only those cells that possess a surface receptor specific for that virus. The matching of a virus with a specific cell type is termed *tropism*. Viruses are tissue and species specific; they infect some species of the animal kingdom and not others. Some viruses only infect humans.

Before most viruses can infect cells and replicate, they must bind specific molecules (ligands) located on their outermost protein coat (envelope) to a receptor on the wall of a tropic cell (Figure 7-1). When the match occurs, the virion penetrates the cell wall and enters the cell's cytoplasm. Upon entry into a cell some viruses shed their envelope by integrating it into the host cell's surface. Once inside the cell the virion undergoes sufficient disintegration to allow segments of its nucleic acids to integrate into the host's genome. DNA viruses

can immediately enter the nucleus and fuse with the host cell's DNA, whereas the RNA viruses remain in the cytoplasm during their intracellular cycle.

The exception to this usual mechanism is the RNA retroviruses that use the host cell's DNA to replicate their RNA genome. Although each family of viruses uses a host cell's replication mechanism in a different way, all viruses alter the usual metabolic and protein synthesis pathways of the host cell in some way to serve their own needs. This process often results in the death of the host cell, allowing the dispersed replicated viruses to infect the cells of adjacent tissue.

LATENCY: A prolonged stage of some viral infections in which the viral core is integrated within cellular components, but its presence is not detectable clinically or with the use of laboratory methods.

Some virions remain harmlessly integrated within the genome of the host cell for prolonged periods. This occurs if the body's immune system attenuates the activity of the virus or if the infection is sufficiently nontoxic that cell death does not occur. The state of attenuated activity has been termed *viral latency*. During this state no apparent clinical lesions or detectable viral antigens are usually expressed on the surface of the infected cell. The unique ability of a virus to avoid detection and destruction by the host immune system and therapeutic agents is particularly common in some members of the herpes

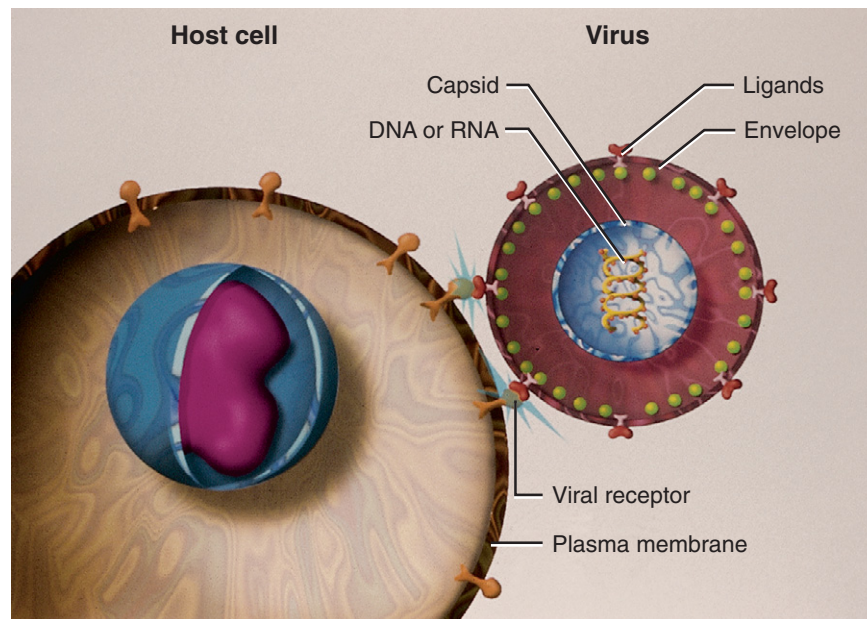


FIGURE 7-1

Basic structure of a virus (*right*) that consists of an outer envelope containing specific binding ligand molecules and an inner capsid containing DNA or RNA chromatin. The virus is achieving tropism, matching its ligand molecules with compatible surface viral receptors of a host cell.

family of viruses but also occurs in other viruses. Viral latency is considered to play an important role in carcinogenesis, acting as a predisposing cofactor necessary for the development of a large array of neoplasms. Latency is considered the reason for long delays in the onset of symptoms of patients infected with the human immunodeficiency virus 1 (HIV-1).

At present, not many effective therapeutic agents are available to curtail viral infections. Consequently, viral infections usually continue until the host's own immune system is capable of dealing with them.

The three most commonly encountered families of viruses within the oral cavity are (1) herpesvirus, (2) coxsackievirus, and (3) papovavirus. In each viral family, one member commonly predominates in occurrence and clinical significance, whereas the rest are less frequently encountered.

HERPES VIRUSES

The herpes family of viruses consists of the following:

- Herpes simplex virus 1 (HSV-1)
- Herpes simplex virus 2 (HSV-2)
- Varicella-zoster virus (VZV)
- Epstein-Barr virus (EBV)
- Cytomegalovirus (CMV)
- Other human herpesvirus (HHV-6, HHV-7, HHV-8)

Of the herpesvirus family, HSV-1, HSV-2, and VZV are neurotropic and EBV, CMV, HHV-6, HHV-7, and HHV-8 are lymphotropic. All herpesviruses are capable of entering and replicating in epithelial cells, and some have been associated with malignancies. HSV-1 and HSV-2 are closely related biochemically and share many common antigens but still have some detectable glycoprotein surface receptors that differ. Although they are closely related, an important difference exists in their biologic activity: HSV-2 possesses oncogenic potential. EBV is also associated with epithelial and lymphoid malignancies. At this time less is known of the biologic activity and oncogenic potential of the HHV-6 and HHV-7 viruses, but HHV-8 is highly associated with the malignant endothelial cells of Kaposi sarcoma.

Herpes Simplex Virus

The core of HSV consists of a single strand of DNA. The chromatid contains more than 80 genes that are divided into three groups according to their function during replication. The large genome of this virus allows it to encode numerous proteins of replication and cellular metabolism, making it able to survive and become ubiquitous in the population. The virus is lytic to human epithelial cells and latent in neural tissue (Figure 7-2). Replication occurs primarily in epithelial cells, resulting

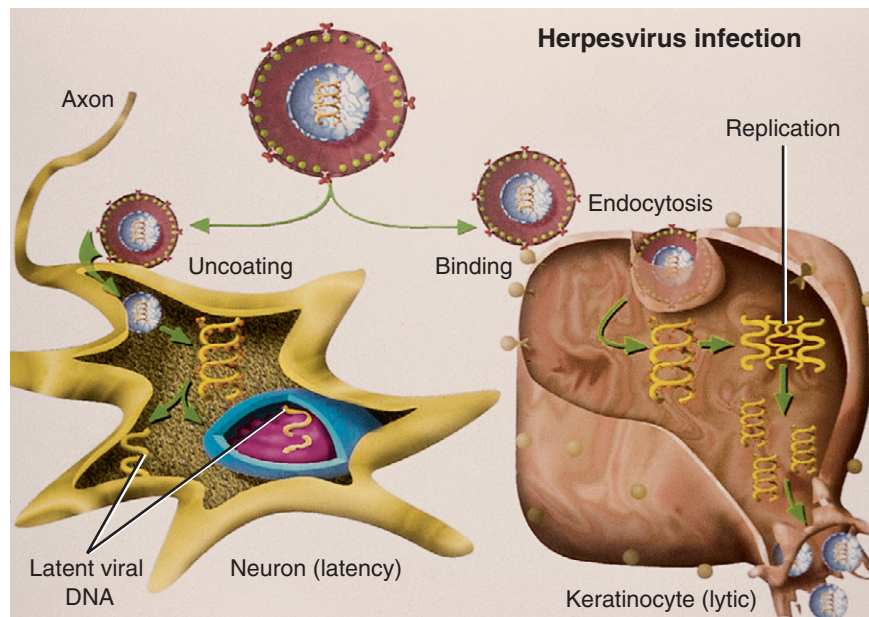


FIGURE 7-2

Two basic types of herpes simplex infection. Lytic infections (*right*) commonly occur after endocytosis of herpesvirus into keratinocyte. Replication and reassembly ensues that overwhelms host cell and causes it to burst, which releases large numbers of viruses. Latent infections (*left*) commonly occur in the cell body of neurons, where viral DNA remains dormant within the cytoplasm or nucleus until activated to replicate and migrate along a neural axis to an epithelial surface.

in cell death and the release of up to 200,000 virions. During release not all of the virions acquire an envelope from the cell's cytoplasmic membrane; the survival time of these virions is therefore very short.

CLINICAL FEATURES

HSV usually enters the body through breaks in the skin, although considerable evidence suggests that it can penetrate intact mucous membranes. HSV-1 occurs primarily in lesions located above the waist, and HSV-2 occurs primarily in lesions below the waist. In approximately 10% of the cases, HSV-2 can be found in oral lesions and HSV-1 can be found in genital lesions.

Patients infected with HSV-1 or HSV-2 experience an initial primary infection followed by a state of latency. Some patients experience repeated recurrences of the infection. Most cases of initial (primary) herpes infection do not produce clinical lesions and have minimal clinical symptoms. Thus most patients are unaware that the virus has entered their body. The virus penetrates the mucosal barrier without visible lesions or symptoms. Because the virus is neurotropic, it infects the peripheral nerves and migrates to a regional ganglion where it remains dormant (latent). In this location it is undetected by the immune system, protected from therapeutic agents, and undiagnosed until activated. Activation results in migration along the nerve axon to surface epithelial cells. This migration can be triggered by a number of factors that may include emotional stress, trauma, cold, sunlight, gastric upset, fever, menstrual cycle, and any number of other factors that result in suppression of the immune system.

Whether patients have primary or secondary occurrences, the incubation period before the emergence of visible lesions ranges between 1 and 26 days; however, it is most commonly 7 to 8 days. Patients usually notice altered sensation in the affected tissue, usually characterized by fullness or a lack of tactile or sensory perception. At this stage and during the vesicular stage that follows, the patient's saliva and genital secretions are highly contagious. It is important to note that the virus may continue to shed into the saliva and other mucosal secretions without active lesions on the epithelial surfaces.

Acute Primary Herpetic Gingivostomatitis

ACUTE PRIMARY HERPETIC GINGIVOSTOMATITIS:

An uncommon clinical presentation of an initial herpes simplex infection in which multiple shallow ulcers are present throughout both the keratinized and gland-bearing intraoral surfaces; accompanied by systemic symptoms of fever, lymphadenopathy, and myalgia.

Approximately 1% of initial oral infections with HSV-1 or HSV-2 occurs as a highly visible and acutely symptomatic primary infection. These infections usually occur in young children, although they also occur

in adults. The initial oral infection can vary and is termed *acute primary herpetic gingivostomatitis*.

Mild forms exhibit multiple small, punctate, shallow ulcers involving both keratinizing and nonkeratinizing oral mucosal surfaces. The ulcers may be confined to the gingiva, or they may involve various sites from the lips and perioral skin to the nasopharynx (Figure 7-3).

Severe forms may present as large, diffuse, whitish ulcers that exhibit scalloped borders and erythematous halos. These lesions lack the characteristic distinct individual punctate appearance of lesions seen in the milder form. The different appearance results from the coalescence of many small ulcers into single, large superficial ulcers.

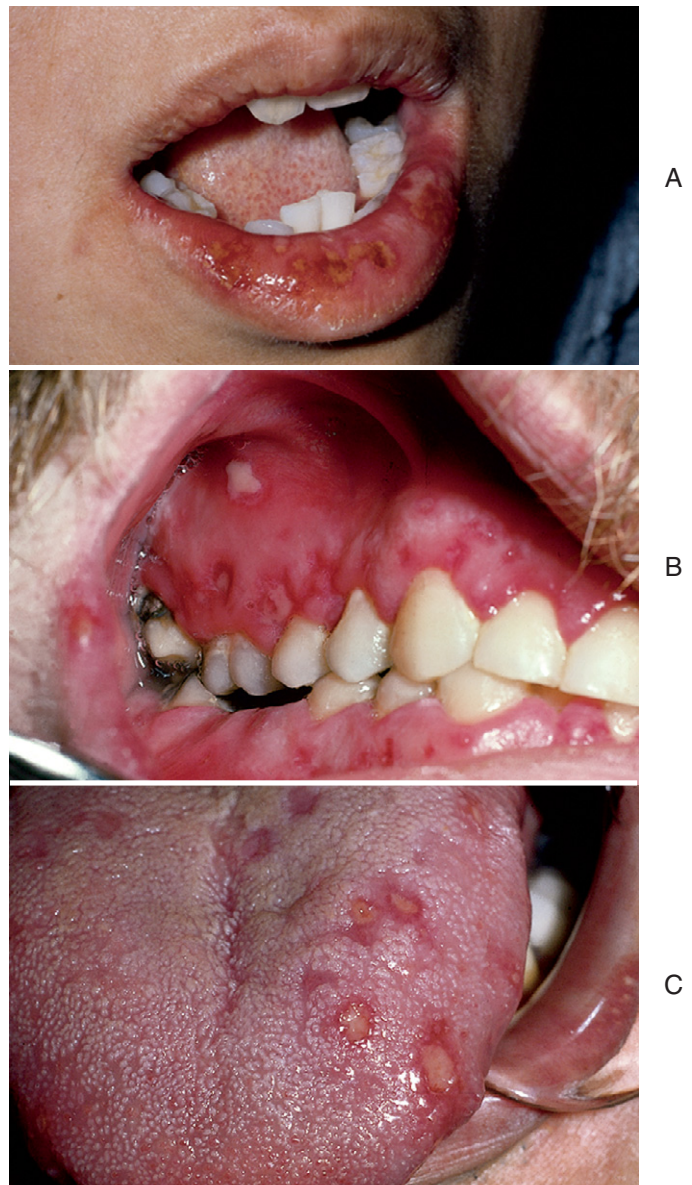


FIGURE 7-3

Acute primary herpetic gingivostomatitis. Multiple shallow punctate lesions on both keratinizing and gland-bearing mucosa. **A**, Lower lip; **B**, gingiva; and **C**, tongue.

In both the mild and severe forms of primary herpetic gingivostomatitis, the patient experiences fever and lymphadenopathy that lasts from 2 to 10 days. Muscle soreness (myalgia) and inability to masticate and swallow food are common problems. If patients are healthy, the signs and symptoms may only last from 2 to 4 days.

In immunocompromised patients a prolonged form of acute primary herpetic gingivostomatitis may develop. Commonly, these patients are receiving chemotherapy for a malignancy, are organ transplant recipients, or have a congenital or acquired immunodeficiency syndrome (AIDS). Surface lesions in these patients are often larger and deeper than those found in relatively healthy patients. In patients with the most severe forms of immunocompetency, such as those with late-stage AIDS, lesions are even deeper, with friable and necrotic centers and accompanied by severe pain.

Secondary Oral Herpes Simplex

RECURRENT ORAL HERPES SIMPLEX. The two main clinical types of recurrent oral herpes simplex infections based on the location of the lesions are (1) recurrent herpes labialis and (2) recurrent intraoral herpes. Recurrent herpes labialis affects the lips, whereas recurrent intraoral herpes involves the palate or maxillary gingiva. Both are commonly associated with recent dental treatment and present as a cluster of small vesicular or punctate lesions. The clinical appearance of the lesions found in the two types differs. Because the labial lesions often involve dry mucosa or skin, they will form identifiable fluid-filled vesicles that rupture, ulcerate, and resolve as crusted brownish lesions (Figure 7-4). Intraoral lesions are found on the wet and fragile mucous membranes and seldom form a clinically visible vesicle. Lesions are punctate with red or white bases that slowly disappear (Figure 7-5).



FIGURE 7-4

Recurrent herpes labialis. **A**, Early stages consisting of fluid-filled viral vesicles. **B**, Late stage demonstrating brownish crusted lesions.



FIGURE 7-5

Recurrent intraoral herpes. **A**, Common intraoral site on posterior palate over greater palatine foramina. **B**, Occasionally encountered gingival lesions.

Recurrent Herpes Labialis

RECURRENT HERPES LABIALIS: *Episodic occurrences of a cluster of vesicles and shallow ulcers localized to the lateral aspects of the lips in patients with latent herpes simplex infections; viruses dormant in ganglia that innervate the lips are triggered by a variety of internal and external factors.*

Herpes labialis is by far the most common form of recurrent herpes simplex infections affecting the lips in 15% to 20% of those who have had a primary infection. It is commonly termed a *cold sore*, because it often occurs after an upper respiratory viral infection. Reactivation of a latent HSV residing in the trigeminal ganglion can be triggered by prolonged exposure to sunlight, trauma and manipulation of the lips, fever, immunosuppression, menstruation, and periods of stress and anxiety. Unfortunately, few definitive treatments are presently available for herpes labialis. Empiric treatments include keeping the lesions soft and covered with an ointment to prevent further spreading and secondary bacterial infection. Although patients experience significant discomfort in the area, they do not exhibit elevated temperatures and seldom exhibit lymphadenopathy.

Recurrent Intraoral Herpes

RECURRENT INTRAORAL HERPES: *Episodic occurrences of an intraoral cluster of symptomatic shallow punctate ulcers, commonly but not exclusively on the mucosa overlying the greater palatine foramina and typically appearing after dental procedures in the area.*

Recurrent intraoral herpes is relatively uncommon and often occurs after dental treatment or injection of a local anesthetic into the area. Some intraoral locations seem to be more prone to recurrent lesions than others. The most common site is the hard palate over the greater palatine foramina. Other intraoral sites include the free and attached gingiva, especially the maxillary gingiva, and the lateral aspects of the tongue. Although the diagnosis of a recurrent intraoral herpes simplex is primarily a clinical one, when lesions occur in the less common sites, they frequently remain undiagnosed until confirmed with a biopsy that includes an incipient vesicle. In patients who are immunosuppressed, the intraoral recurrent lesions are often substantially larger, deeper, and accompanied by fever and lymphadenopathy, resembling a prolonged acute primary form of the disease. No known treatment exists for recurrent intraoral herpes simplex. Establishing the diagnosis and alleviating the patient's concerns about a more serious disease are usually sufficient.

Neonatal Herpes Simplex Virus

Neonatal HSV infection is infrequent, with an incidence ranging from 1 in 3500 to 1 in 20,000 births, depending on the population. Neonatal HSV infection is

much more frequent in infants born to mothers experiencing a primary HSV infection, with an incidence approaching 50%, whereas infants born to mothers experiencing recurrent HSV infection have an incidence of less than 3%. Neonatal infections are clinically categorized according to the extent of the disease. Infections commonly involve only the skin, eyes, and mouth but may include the central nervous system (CNS) and several organs, including the liver, lungs, and adrenals. Caesarean section is often recommended for those women who have clinical evidence of active herpes lesions on the cervix or vulva at the time of delivery. The current recommendation for treatment of neonatal HSV is intravenous (IV) infusion of acyclovir and supportive care. Prognosis is dependent upon the extent of disease and the efficacy of treatment, with highest rates of morbidity and mortality in widely disseminated infections.

Herpetic Whitlow

HERPETIC WHITLOW: *A primary or secondary herpes simplex infection localized to the hands or fingers and acquired by direct contact with an active lesion.*

Before the time when gloves were required for all clinical procedures, herpetic whitlow was a common occurrence on the hands of health care workers. In addition to infection by direct contact with oral lesions, herpetic whitlow can occur by autoinoculation from oral or genital lesions. Lesions are usually vesicular or pustular and surrounded by a wide zone of erythema (Figure 7-6). Throbbing pain, high fever, and regional lymphadenopathy of the arm or axilla are common. The symptoms are often of sufficient severity to incapacitate the patient for 1 or more weeks. Restricting contact with others is usually advisable, because lesions on the fingers



FIGURE 7-6
Herpetic whitlow. Painful, inflamed herpetic lesion on finger.

are highly contagious. Immediate treatment with oral famciclovir has been shown to be effective in reducing the symptoms and duration of the lesions.

HISTOPATHOLOGY

During the prodromic stage before vesicle formation, the infected individual keratinocytes initially accumulate fluid and swell, giving the cytoplasm a vacuolated appearance termed *ballooning degeneration*. Some cells exhibit nuclear changes consisting of margination of the chromatin and the presence of large eosinophilic intranuclear inclusion bodies; many will undergo syncytial changes resulting in multinucleated epithelial giant cells (Figure 7-7, A). Clinically visible papules and vesicles develop when the accumulation of intracellular and intercellular edema results in lysis of a number of adjacent cells. In addition to the numerous ballooned cells and virus particles, multinucleated epithelial giant cells are present within the fluid (Figure 7-7, B). Although the content of most mucosal vesicles will clinically appear as a clear transudate, purulent exudate is occasionally present on the skin and pustules will develop. Pustules or vesicles are seldom seen on mucosal surfaces, because the epithelial layer is fragile and readily ruptures, leaving a punctate and shallow erosive lesion.

Microscopic examination of the contents of an intact vesicle reveals a fluid-containing fibrin, ballooning degenerated and multinucleated epithelial cells, and some acute inflammatory cells (Figure 7-7, C). The large number of liberated viruses is not visible with light microscopy. The base of the lesion may exhibit an intact basal cell layer or, more commonly, a thin inflamed zone of connective or granulation tissue (or both).

DIAGNOSIS

Diagnosis of a herpes simplex infection is usually based on the clinical findings. When the diagnosis is not readily apparent, one or more of the following laboratory procedures may be useful.

Biopsy. Ideally, an excisional biopsy of an intact vesicle is obtained. The viral cytopathic effects (CPE), including cellular ballooning degeneration, multinucleated epithelial cells, and nuclear inclusions, can be observed in routine hematoxylin and eosin (H&E)-stained tissue slides. Immunostains using monoclonal antibodies applied to the fixed tissue sections can be used to identify specific types and subtypes of the herpesvirus.

Cytologic smear. The clinician obtains the specimen by puncturing an intact vesicle and expressing the vesicular (blister) fluid onto a glass slide or by mechanically removing cells from the base or edges of a lesion and smearing them onto microscopic slides. The smears are stained and examined for the CPE of the virus on the epithelial cells. The CPE observed in-

clude the presence of inclusion bodies, ballooning degeneration, and multinucleation of epithelial cells (see Figure 7-7, B). The test is not specific for HSV, because similar CPE are found in the epithelium of VZV lesions.

Culture. The culture specimen is best obtained from intact vesicles or pustules. Contents of a needle aspiration are optimal, but a cotton swab may also be used to directly inoculate a tissue culture. The cultured cells are examined for CPE on epithelial cells. High concentrations of the virus will produce changes in the cultured cells after 24 hours; the mean time for a positive test is 1 to 3 days.

Fluorescent antibody. The specimen consists of smears or suspensions of cells stained with antibodies against HSV-1 and HSV-2 antigens. Antibodies are labeled with a fluorescent dye that is visible microscopically or with spectroscopic instruments. This method is not as sensitive as the culture method.

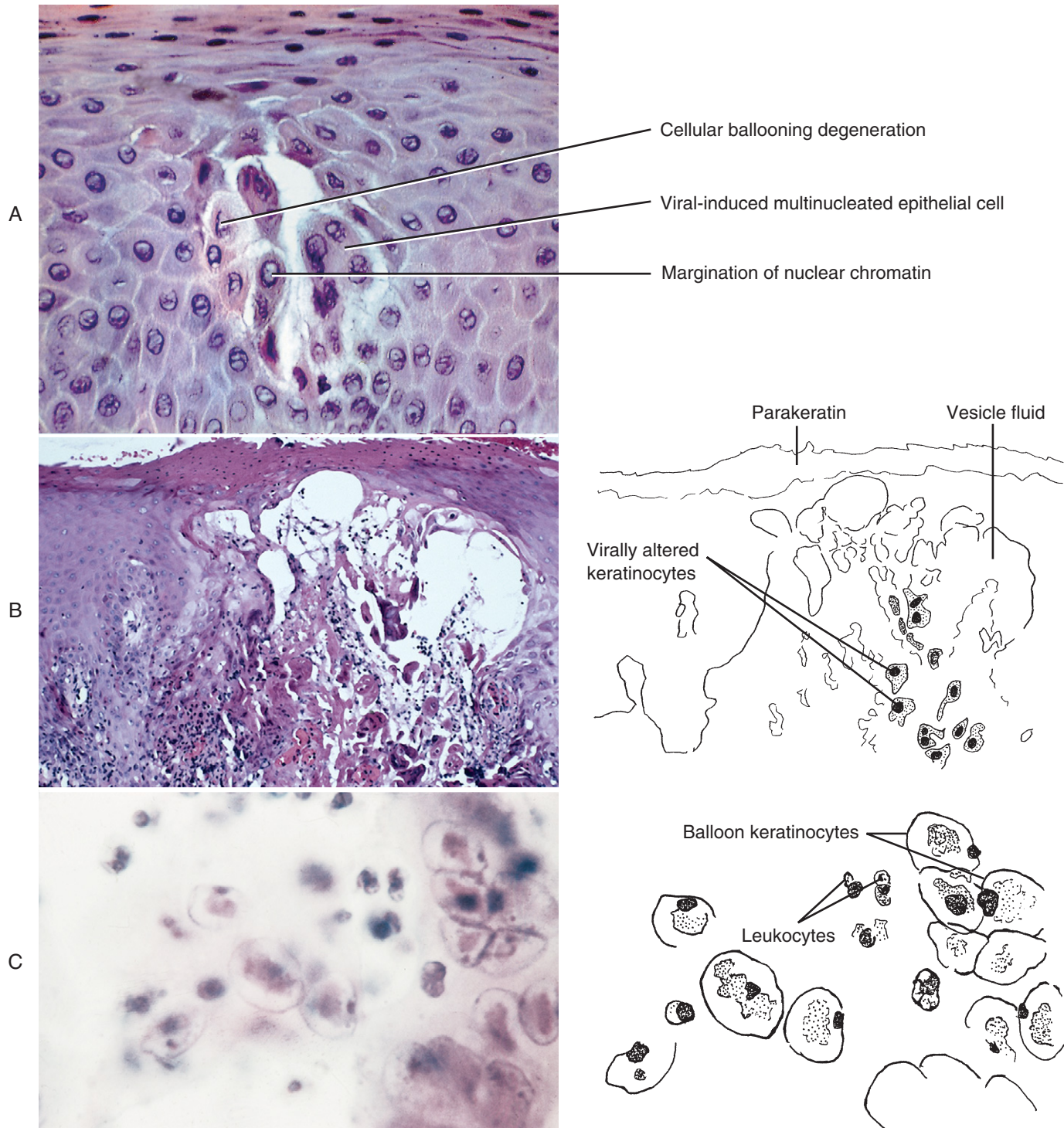
Serology. This is an indirect test in which blood samples are tested to detect antibody levels in the serum against specific viral antigens. Serology is sensitive only for primary infections, because levels of circulating antibody in recurrent disease are usually too low to be detected.

TREATMENT

Treatment of HSV infections varies with the type and location of the infection and the systemic condition of the patient. In general, resolution of viral lesions depends on the competency of the patient's immune system. When taken systemically, therapeutic antiviral agents such as acyclovir, famciclovir (penciclovir), and valacyclovir can be of help, particularly in immunocompromised patients. Acyclovir is most effective in the treatment of primary genital lesions and only marginally effective for recurrent genital lesions or primary and recurrent oral infections. Treatment of the more generalized oral lesions of primary infections is mostly palliative, using soothing oral rinses and analgesics. Antibiotics are often prescribed for the prevention of secondary infections.

The use of acyclovir or other similarly acting agents has been shown to shorten the duration of the episode of the primary type of oral infection. Treatment of recurrent labial and intraoral lesions in immunocompetent patients has not been uniformly successful.

Of the systemic antiviral agents available for recurrent HSV, only acyclovir and famciclovir (penciclovir) appear to have some effect. In a study when both were used topically in a cream base and applied during the early prodromal stage, 1% penciclovir was shown to be slightly more effective than 5% acyclovir in reducing the healing time, viral shedding, and the duration of the painful phase.

**FIGURE 7-7**

Herpes simplex. Early and late stages of intraepithelial viral vesicle formation. **A**, Incipient vesicle formation early in prodromal stage before presence of a clinically visible vesicle exhibiting ballooning degeneration, nuclear margination, and multinucleation of the spinous layer of keratinocytes (viral cytopathic changes). **B**, Fully developed but intact intraepithelial viral vesicle that contains fluid, virally altered keratinocytes, large numbers of viruses, and necrotic debris. **C**, Photomicrograph of cytologic smear of viral vesicle contents that reveals enlarged and ballooned keratinocytes and associated leukocytes.

Varicella-Zoster Virus

VZV is a member of the herpes family of viruses and shares many features with the HSV. The primary infection of VZV is known as *varicella* or **chicken pox**; the recurrent disease is termed *herpes zoster* or **shingles**. Primary infections are followed by a period of latency during which the neurotropic virus resides in the regional ganglia. Later, if the host's immune system is overwhelmed or suppressed, the virus may emerge to produce recurrent disease along a specific dermatome. Like HSV, the epithelial lesions are intraepithelial fluid-filled vesicles on the skin or mucosal surfaces. VZV differs from HSV in that its initial mode of contact is by inhalation of droplets that enter the body through the respiratory system. In this location, replication occurs before systemic spreading via the blood stream (viremia), after which numerous skin and mucosal eruptions appear. The VZV is structurally similar to other members of the herpes family, differing by having only minor variations in the ratio of guanine and cytosine amino acids in its genome.

Varicella (Chicken Pox)

VARICELLA: Primary infection of the VZV acquired during childhood that produces a generalized symptomatic maculopapular rash of the skin, malaise, fever, and minor lesions throughout the oral cavity.

CLINICAL FEATURES

Varicella is the initial infection of VZV and is usually acquired in childhood. Unlike HSV infections the primary infection is usually symptomatic and includes fever, headache, malaise, sore throat, and lung congestion. In the Western world, 90% of the adult population will contact the virus and harbor it in its latent form. Over 50% of those initially affected will be children between the ages of 5 and 9. After an incubation period of approximately 2 weeks, patients develop a cutaneous hemorrhagic maculopapular rash accompanied by malaise and a low-grade fever. Lesions quickly progress to vesicles and pustules that rupture and become crusted (Figure 7-8). For approximately 1 week, new lesions will continue to appear so that a mixture of lesions at various stages of development and resolution is always present. Small numbers of vesicular lesions are usually present on the oral mucosa, including the tongue, buccal mucosa, gingiva, palate, and oropharynx. The oral vesicles rupture early and are usually seen as small ulcers that closely resemble aphthous ulcerations. The oral lesions are not particularly painful. Occasional pustular skin lesions become secondarily infected and may heal as a small, depressed scar (pock). When acquired in adulthood the disease may be severe and progress to interstitial



FIGURE 7-8

Varicella (chicken pox). Crusted lesions (pox) of skin of the late stage of a primary infection of the varicella-zoster virus (VZV) in a young patient.

pneumonia. If patients are immunocompromised, widespread dissemination can result in death.

Herpes Zoster (Shingles)

HERPES ZOSTER: A regional occurrence of VZV that appears as vesicular eruptions of the skin or mucosa in a distinctive unilateral pattern; pain persists for prolonged periods after lesions heal.

Herpes zoster is the recurrent form of a varicella infection. It affects 10% to 20% of the population and can occur at any age, but it is more common in the elderly and the immunocompromised. Factors that decrease immune function, such as human immunodeficiency virus (HIV) infection, chemotherapy, malignancies, and chronic corticosteroid use, increase the risk of developing herpes zoster. The virus is believed to infect the dorsal root ganglia during the primary infection, where it remains latent until reactivated. The frequency and severity of herpes zoster in older people appears to be the result of an age-related decline in VZV-specific T cell-mediated immunity. On the skin the predominant clinical feature is a unilateral linear vesicular rash outlining the cutaneous distribution of the affected peripheral nerves, most commonly those of dermatomes T3 to L3. Coalescence of the vesicles, followed by crusting, occurs quickly.

When herpes zoster involves the trigeminal nerve, unilateral facial and oral lesions may develop along the ophthalmic, maxillary, and mandibular distribution of the nerve (Figure 7-9, A). Lesions on the intra-oral mucosal surfaces are sharply and distinctively unilateral along the nerve distribution (Figure 7-9, B). The mucosal lesions develop as fragile vesicles that rupture

**FIGURE 7-9**

Herpes zoster (shingles). **A**, Multiple unilateral painful vesicles follow the mandibular branch of the trigeminal nerve. **B**, Multiple vesicles on an erythematous base with a unilateral, sharp line of demarcation that corresponds to the nerve distribution of the palate.

easily and are usually seen as crateriform ulcers that may persist from 2 to 3 weeks, usually healing within 1 month.

Lesions produce pain on both skin and mucous membranes. During the few days before the eruption of the vesicles, the patient experiences pain, paresthesia, and dysesthesia in the affected dermatome. When lesions appear, patients usually experience a stinging form of pain. In older patients the pain may persist for 1 month or more after the lesions have healed. This condition is termed *postherpetic neuralgia* and is characterized by burning and severe pain. The healed area may remain hypersensitive for months or years and can be highly debilitating. In the immunocompromised patient (in addition to developing deeper and more widespread lesions) the condition may become chronic, with persistent pain and occasional CNS involvement and death. In Ramsey Hunt syndrome, patients develop a triad of conditions consisting of ipsilateral facial palsy, external auditory canal lesions, and loss of taste in the anterior two thirds of their tongue.

HISTOPATHOLOGY

The tissue changes in lesions of varicella and herpes zoster are essentially the same as in those of HSV. During the prodromal period epithelial cells containing replicating viruses exhibit cytoplasmic swelling because of intracellular edema (ballooning degeneration), margination of nuclear chromatin, and the formation of intranuclear inclusion bodies. Multinucleation of epithelial cells will also be seen when intraepithelial vesicles have formed. The postvesicular ulcer is similar to any other shallow ulcer character-

ized by a fibrinopurulent exudate covering a zone of granulation tissue.

DIAGNOSIS

The presence of unilateral lesions along dermatomes of the peripheral nerves is pathognomonic for herpes zoster. In varicella or herpes zoster when the classic distribution of lesions is not present, as often occurs in immunocompromised patients, and when involvement is more diffuse, one or more of the following laboratory techniques may be diagnostically helpful.

Cytologic smear. The specimen consists of fluid obtained from vesicles and smeared on slides. The presence of epithelial cells that exhibit cytopathic changes including ballooning degeneration, intranuclear inclusions, and multinucleation of epithelial cells are positive findings of a viral infection. Unfortunately, HSV infection will give a similar result.

Culture. Swabs of vesicle fluid or lesional tissue are cultured in the same manner as for HSV.

Direct immunofluorescent antibody. Microscopic examination of a sample of lesional tissue is reacted with an antibody to the VZV, labeled with fluorescein dye, and viewed with ultraviolet (UV) light.

Serology. The most frequently used are the fluorescent antibody to VZV membrane antigen (FAMA) and the enzyme-linked immunosorbent assay (ELISA) tests that measure the level of VZV antibody circulating in the patient's blood. They are mainly used to document the presence of the virus and the severity of the infection and are most effective in primary infections of varicella when antibody levels are high. Recurrent lesions of herpes zoster will only have detectable circulating antibodies several weeks after the appear-

ance of lesions and in only 50% of the cases. In those cases, polymerase chain reaction (PCR) of vesicle fluid may be of assistance.

TREATMENT

Herpes zoster is usually treated with orally administered acyclovir. Other antiviral medications include famciclovir and valacyclovir. The antiviral medications are most effective when started within 72 hours after the onset of the rash. The addition of an orally administered corticosteroid can provide modest benefits in reducing the pain of herpes zoster and the incidence of postherpetic neuralgia. Ocular involvement in herpes zoster can lead to rare but serious complications and generally merits referral to an ophthalmologist. Patients with postherpetic neuralgia may require narcotics for adequate pain control. Tricyclic antidepressants or anticonvulsants, often given in low doses, may help to control neuropathic pain. Capsaicin, lidocaine patches, and nerve blocks can be used in selected patients.

Epstein-Barr Virus

EBV is a member of the herpesvirus group and exhibits tropism for human B lymphocytes. By means of the lymphocytes the virus can gain passage to the epithelial cells of the oropharynx and nasopharynx. The mechanism for infection of epithelial cells of the lateral borders of the tongue in HIV-positive patients is unknown. EBV is known to be a causative factor in **infectious mononucleosis (IM)**, Burkitt lymphoma, and nasopharyngeal carcinoma. The EBV virus has recently been associated with the inverted papilloma of the nose (in addition to the human papilloma virus [HPV] that is frequently present in that lesion). In patients with acquired and congenital immunodeficiency conditions, EBV is found in B-cell lymphomas and in white lesions (hairy leukoplakia) on the lateral borders of the tongue. The structure of EBV is similar to that of HSV and VZV and has an array of detectable antigens specific for the virus and some that are differentially expressed during an infectious process. The target cell receptors are located on the surface of the B lymphocytes; after binding with EBV they undergo rapid mitosis that in turn activates T lymphocytes. The heterophile antibody is a byproduct of the rapid increase in B lymphocytes. It is an IgM class antibody that recognizes and binds the Paul-Bunnell antigen of sheep and bovine red blood cells. This is a particularly useful test for the diagnosis of IM. Antibodies to the other EBV antigens are also used diagnostically. These include the Epstein-Barr virus nuclear antigen (EBNA), which is a late antigen found in infections; early antigens, EA-R found in Burkitt lymphoma and ER-D

found in IM; and the viral capsid antigen (VCA), which is a late antigen found in all cells actively producing a virus. The B lymphocyte stimulation of T lymphocytes is considered part of how the body controls infection by the virus. Patients with transient or permanently impaired T-cell function have difficulty coping with EBV, resulting in chronic states of EBV infection. Alteration of this mechanism may be responsible for the development of some manifestations of AIDS.

CLINICAL FEATURES

EBV is transmitted through saliva containing the virus, which was shed from the epithelial cells of the oropharynx of infected patients. Because nearly 90% of the adult population harbors the EBV virus and because it is periodically shed in the saliva, opportunities for contact are frequent.

INFECTIOUS MONONUCLEOSIS: *A debilitating EBV infection of B lymphocytes characterized by fatigue, malaise, lymphadenopathy, fever, and other symptoms that persist for prolonged periods; it occurs primarily in young adults.*

When the initial infection is acquired during early childhood, it is mild and usually subclinical. In contrast, when acquired in adolescence or young adulthood, it frequently leads to the development of IM. IM can be a severe, debilitating condition characterized by lymphadenopathy, malaise, pharyngitis, fatigue, fever, hyperplastic tonsils, thrombocytopenia, and splenomegaly. Intraorally, patients often exhibit multiple petechiae of the soft palate (Figure 7-10). The condition generally persists for 4 to 6 weeks; however, lymphadenopathy and the minor degrees of fatigue and malaise persist for several months.



FIGURE 7-10

Infectious mononucleosis. Multiple coalesced petechiae of the soft palate in a young patient.

HISTOPATHOLOGY

Tissue from either the tonsils or enlarged lymph nodes exhibits germinal hyperplasia and large, abnormal, nonneoplastic T lymphocytes. The aberrant lymphocytes are basophilic with a vacuolated cytoplasm and large, kidney-shaped nuclei.

DIAGNOSIS

Diagnosis is based on a combination of clinical findings, a positive heterophil antibody test, and Epstein-Barr virus capsid antigens (EBVCA). Cultures for EBV are not available on a routine diagnostic basis.

TREATMENT

Acyclovir is of little help in relieving symptoms and in controlling the course of diseases caused by EBV. Rest and analgesia are the primary supportive measures used by clinicians. Restricting periods of physical exertion is important to reduce the possibility of splenic rupture. It is not necessary to isolate patients with IM.

Cytomegalovirus

CMV is similar in structure to the other members of the herpes family of viruses. It is primarily acquired as an infection in early childhood, with individuals carrying it for life in a latent form. The infection usually remains silent until T lymphocyte-mediated immunity is compromised, as occurs with immunosuppression for management of organ transplant or other forms of acquired immunodeficiency (AIDS). If contracted during fetal development from an infected mother, stillbirth is a possible outcome. Up to 1% of newborns have been found to carry the virus. CMV is found in saliva, breast milk, urine, and semen. It is transmitted through blood-to-blood and intimate contacts and organ transplants. CMV has a latency period during which it may reside or replicate in the epithelial cells of the kidney or oropharynx.

CLINICAL FEATURES

In postneonatal infected children and young adults, the virus is usually transmitted through the saliva of infants. In these patients the symptoms consist of mild pharyngitis, malaise, fever, and lymphadenopathy. The most common distinguishing feature of a CMV infection is that although it appears clinically much like IM, it is heterophil antibody negative. Blood smears may exhibit the same atypical lymphocytes as observed in IM but usually no clinical evidence of cervical lymphadenopathy. Reactivated infections may occur later during periods of reduced immunocompetence or immunosuppression. Rare severe infections can result in hepatitis, pneumonia, thrombocytopenia, or encephalitis. CMV can be an important viral pathogen in organ transplant patients with

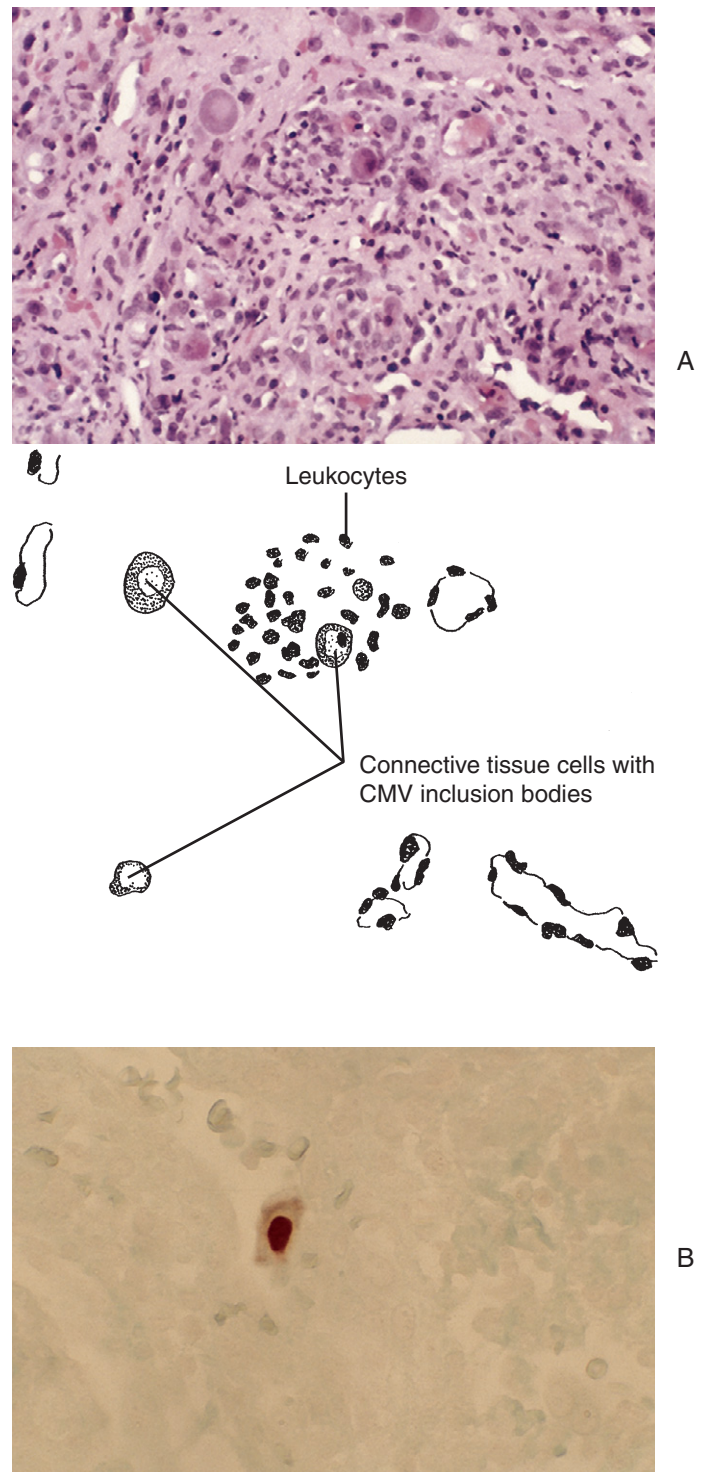


FIGURE 7-11

Cytomegalovirus ulcer. **A**, Photomicrograph of a zone of granulation tissue at the base of an ulcer containing enlarged cells with intranuclear inclusion bodies in routine hematoxylin and eosin (H&E)-stained tissue. **B**, Tissue with an immunoprobe for cytomegalovirus using DNA in situ hybridization (red-stained cell).

the transplanted organ itself being particularly susceptible. In patients with AIDS, CMV infections can be fatal.

HISTOPATHOLOGY

Characteristic tissue changes are found primarily after reactivation in immunosuppressed patients or in patients who have died of lymphoma or leukemia. In these patients parenchymal and individual cells within the surrounding connective tissue are 2 to 4 times larger than normal cells (cytomegaly) and contain large intranuclear inclusion bodies measuring 8 to 10 µm (Figure 7-11, A). The characteristic cells can be found in a variety of organs, including salivary gland, lung, liver, kidney, intestine, and CNS. The presence of CMV can be revealed using DNA in situ hybridization (Figure 7-11, B).

TREATMENT

No reliable treatment or vaccine is presently available. In immunocompromised patients, intense and prolonged regimens of ganciclovir and foscarnet seem to offer some degree of effectiveness.

Human Herpesvirus 6, 7, and 8

HHV-6 and HHV-7 are newly recognized ubiquitous human viruses first discovered in patients with AIDS or lymphoproliferative disorders. Much more information is available about the clinical characteristics of infection of HHV-6 than HHV-7.

HHV-6 is secreted in the saliva of nearly all children and is most commonly manifested as a nonspecific highly febrile illness. Some develop the classic manifestations of roseola infantum or exanthem subitum. The most common complication in children is febrile seizures. In adults, HHV-6 is found in the lymphocytes of lymphoproliferative diseases and has been linked to neurologic diseases such as encephalitis and multiple sclerosis.

HHV-7 is similar to HHV-6 in genetic organization and structure, but little is known of its clinical characteristics, its ability to cause disease in children, or its reactivation in adults.

Several lines of evidence indicate that HHV-8 is strongly associated with the development of Kaposi sarcoma (KS) in AIDS patients. HHV-8 DNA is invariably found in KS spindle cells and not regularly detected in most other malignancies. The virus has been found to encode and induce several cytokines and angiogenic factors. The role of HHV-8 in the pathogenesis of KS may be rather complex and different from other virus-induced malignancies. The virus is also present in many cases of Castleman disease when it is associated with an HIV infection.

TREATMENT

A series of antiviral compounds have been approved for clinical use in the treatment of herpesvirus infections of HHV-6, HHV-7, and HHV-8. They are acyclovir, valacyclovir, penciclovir, famciclovir, ganciclovir, foscarnet, and cidofovir. At present, the most potent compounds with the highest antiviral selectivity index are foscarnet and cidofovir for HHV-6 and HHV-7 and cidofovir and ganciclovir for HHV-8.

COXSACKIE VIRUSES

The coxsackieviruses are part of the picornavirus family, one of the largest and most prevalent of the RNA viruses. This family also includes the rhinoviruses of the common cold. Because the coxsackievirus has a portal of entry through the oropharynx and gastrointestinal (GI) tract, it is part of the subgroup of enteroviruses that also includes the polioviruses and the echoviruses. Coxsackie viruses have a wide range of tissues for which they exhibit tropism. Included among the tissues is the epithelium of the oropharynx. There are two types coxsackievirus A and coxsackievirus B, each with multiple subtypes (A1 to A23 and B1 to B6). The diseases affecting the oral region are of the coxsackievirus A group. The major ones are herpangina (most subtypes); hand, foot, and mouth disease (A9, A16); and lymphonodular pharyngitis (A10).

Herpangina

HERPANGINA: A nontreatable mild infection caused by a mixture of coxsackievirus A localized to the posterior soft palate and nasopharynx that consist of multiple small shallow ulcers resembling a herpetic infection that lasts for approximately 1 week.

Herpangina is a misnomer because it is not caused by a herpes virus as the name implies. It is transmitted by inhalation of airborne droplets or by contacts with saliva containing coxsackievirus A. The virus can survive outside the body for 2 to 4 hours. Herpangina frequently occurs in outbreaks, particularly among schoolchildren. Nearly all of the subtypes can be isolated from oral lesions. Patients usually develop a permanent immunity to a particular member of a subgroup but not to other members.

CLINICAL FEATURES

Symptoms are usually mild and of short duration, lasting no more than 1 week. Patients complain of a sore throat and difficulty swallowing. There may be a mild fever and some malaise. Small vesicular or punctate lesions with a white base will be present on the posterior soft palate near the uvula and anterior fauces of the

**FIGURE 7-12**

Herpangina. Multiple small vesicular and punctate lesions of the posterior soft palate and nasopharynx.

tonsils (Figure 7-12). The lesions rarely appear anterior to this region. This is of particular help in distinguishing this entity from other viral diseases and herpetiform aphthous ulcers.

TREATMENT

Because the symptoms are mild and of short duration, no specific treatment is necessary.

Hand, Foot, and Mouth Disease

HAND, FOOT, AND MOUTH DISEASE: A highly contagious systemic infection of coxsackievirus A subtypes (usually 9 and 16) of limited duration in which vesicular eruptions occur on the palms of hands, soles of feet, and mucosa of the anterior part of the mouth.

Hand, foot, and mouth disease is usually caused by subtypes 9 and 16 of coxsackievirus A, but others have also been isolated. It is highly contagious and occurs in local outbreaks, mostly among children in the 1- to 5-year age group.

CLINICAL FEATURES

During the short incubation period the patient experiences malaise, low-grade fever, nausea, and an eruption of small vesicles on an erythematous base on the palms of the hands and the feet (Figure 7-13, A and B). Within 1 to 2 days oral vesicles and ulcers appear on the mucous membranes and are usually confined to the anterior part of the mouth (Figure 7-13, C). Lesions are uncommon in the oropharyngeal area, which differs from herpangina.

**FIGURE 7-13**

Hand, foot, and mouth disease. Eruption of small vesicles on the palms of the hands (A), feet (B), and lower lip (C) of a young patient. (Courtesy Dr. W. Goebel.)

HISTOPATHOLOGY

The tissue contains intraepithelial vesicles and epithelial cells exhibiting ballooning degeneration. Because coxsackieviruses are RNA types, infected cells usually contain microscopically visible eosinophilic intracytoplasmic inclusion bodies.

TREATMENT

Hand, foot, and mouth disease is self-limiting and lasts from 1 to 2 weeks with only mild symptoms. No specific treatment is necessary.

Acute Lymphonodular Pharyngitis

ACUTE LYMPHONODULAR PHARYNGITIS: A localized infection of coxsackievirus A (subtype 10), consisting of yellow or white papules surrounded by an erythematous zone confined to the lymphoid tissues of the posterior soft palate and nasopharynx that lasts from 1 to 2 weeks.

Acute lymphonodular pharyngitis is caused by the coxsackievirus. It occurs as an endemic outbreak among schoolchildren. The condition does not produce the usual vesicles and superficial ulcers seen in other viral lesions; therefore it is often misdiagnosed or overlooked.

CLINICAL FEATURES

The characteristic lesions are located in the same anatomic region of the mouth as herpangina. They appear as raised white or yellow papules or nodules that do not ulcerate. Usually, multiple lesions are present that are surrounded by an erythematous zone. Typical locations include the uvula, soft palate, anterior fauces, and posterior oropharynx. Lesions are preceded by a 2- to 10-day incubation period accompanied by a mild headache, fever, and sore throat. The duration of the symptoms and lesions varies from 1 to 2 weeks.

HISTOPATHOLOGY

The lesions consist of raised epithelium because of underlying, densely packed lymphocytes, which in some areas may still have identifiable lymphoid germinal centers. The overlying epithelium may contain intracytoplasmic inclusion bodies.

TREATMENT

The disease is self-limiting and mild in nature; no specific treatment is required.

TOGAVIRUS

The togavirus is an enveloped, single-stranded RNA virus consisting of four major groups. The Rubivirus group is the only important member of this family, because it has the rubella virus as its only member. The disease caused by this virus is also referred to as *rubella* or commonly as *German measles*. Most members of the togavirus family do not infect humans. Although the rubella virus causes only a mild exanthematous skin rash in children, it can cause serious developmental defects in a developing fetus during the first trimester of pregnancy.

Rubella

RUBELLA: A systemic viral infection beginning in the respiratory tract and extending to the circulatory system; produces a papular skin rash, fever, and malaise that last from 1 to 2 weeks; capable of producing congenital defects during pregnancy.

CLINICAL FEATURES

Rubella is a respiratory virus, differing from the other members of the togaviruses. It infects by entering the upper respiratory system and lungs, spreading to the local lymph nodes and eventually into the blood stream as a viremia. This stage represents the prodromal period, which lasts approximately 2 weeks. At this point, even before the emergence of a rash, the virus is shed and can be spread through the inhalation of respiratory droplets. During the prodromal period and subsequent viremia, fever, malaise, and headache are common. When the disseminated virus reaches the skin, a papular rash develops and lasts for another 1 to 2 weeks. No specific oral lesions are noted on the mucosa. The spreading of the rubella virus to pregnant women during endemic outbreaks is of major concern. When pregnant women contract rubella, particularly when their immunity is less than adequate, the virus is allowed to enter the fetal circulatory system, producing defects in the developing tissues and organs. Major risk of a developmental defect is present until the twentieth week of gestation. Common congenital defects include deafness, degrees of blindness, and cardiovascular alterations. In severe cases, miscarriage or stillbirths can occur.

TREATMENT

Rubella that occurs during childhood, when symptoms are mild, requires no specific treatment. At present, prevention is the main thrust in the management of outbreaks of rubella. Dependable vaccines have recently been developed and are being made widely available in an attempt to eradicate the virus from the human population. Eradication is thought to be an attainable goal, because the virus has one subtype and infects humans only. Expectant mothers who are not sure of their immune status to the rubella virus should be vaccinated as a preventive measure.

PARAMYXOVIRUSES

The paramyxoviruses are large RNA viruses. The two most prominent members are (1) measles and (2) mumps viruses. Both viruses are transmitted through saliva and therefore have implication to health care workers who must recognize the presence of these diseases in their patients to prevent transmission. The viruses are easily

and rapidly transmitted. Since 1977 the United States has had a mass vaccination program against measles, mumps, and rubella (administered after an infant is 15 months old).

Before the development of these vaccines, regular epidemics of these viral diseases were widespread. This has largely disappeared, with periodic resurgence occurring only when failure to immunize selected populations of infant and young children occurs.

Measles

MEASLES: A highly contagious systemic viral infection contracted through the respiratory system and spread through the circulatory system, with a predilection for skin blood vessels that produce a skin rash and sometimes pneumonia and encephalitis.

Measles is one of the most severe and widespread of the childhood exanthematous diseases. The virus enters the body through the respiratory system and undergoes rapid replication within the respiratory epithelium before extending to the regional lymph nodes, invading white blood cells and spreading throughout the body via the circulatory system. The virus has a predilection for blood vessel walls, particularly those of the skin, and produces the characteristic erythematous rash.

CLINICAL FEATURES

Excruciating headaches, a rash, photophobia, high fever, and a cough are the hallmarks of a prerash measles infection. After an incubation period of 2 to 4 days in which the lungs are infected, the virus spreads to the brain, superficial blood vessels, conjunctiva, urinary tract, GI tract, and oral mucosa. Symptoms emanate from all sites during the next week. Lesions referred to as *Koplik spots* infrequently occur on the oral mucous membranes, usually before the development of a skin rash.

They are usually asymptomatic, transient in nature, and often overlooked, appearing as small white papules on an erythematous base on the buccal mucosa. Palatal petechiae and generally inflamed mucous membranes and gingiva are also present during the peak of the infection. The possible complication of fatal forms of encephalitis or viral pneumonia is of concern. Patients become contagious approximately 4 days before they feel ill, making intervention to prevent spread of the virus difficult. A skin rash eventually appears, indicating the presence of the disease.

TREATMENT

Measles is treated symptomatically with analgesics, fluids, and rest. Patients who develop otitis media and pneumonia may be given antibiotics. Immunocompromised

patients are administered immune serum globulin, which is most effective if administered within 6 days of the initial exposure. Most of the treatment strategy is aimed at preventing measles from spreading.

Mumps (Epidemic Parotitis)

MUMPS: A viral infection contracted through the respiratory system that primarily affects one or more major salivary glands with swelling and pain; occasionally affects other organs and produces fever and malaise.

The mumps virus is a paramyxovirus that has only one subtype. It is worldwide in distribution and, where no vaccination programs exist, occurs throughout the year. Evidence of infection is present in 85% to 90% of individuals by the age of 15, although not all will have obvious symptoms. The virus is spread through saliva and nasal droplets and is communicable during the prodromal period 2 weeks before the onset of clinical signs and symptoms. It infects and replicates in the respiratory mucosa before disseminating to the salivary glands, CNS, testes, ovaries, pancreas, and occasionally the eyes and middle ear. Usually, involvement of tissues other than the parotid glands is not severe.

CLINICAL FEATURES

Patients with classic mumps manifest swelling of one or both parotid glands in addition to the usual signs and symptoms of viral infections such as headache, fever, and malaise. In some patients the submandibular glands will also be involved. The enlarged glands are very painful, especially at mealtime. A noteworthy clinical sign is the elevation of the earlobe on one or both of the affected sides when it is viewed from behind the patient. This is indicative of involvement of the tail of the parotid gland. This sign helps to differentiate mumps from nonparotid causes of facial swelling (dental abscess, associated cellulitis). Intraorally the papilla over the opening of Stensen duct on the buccal mucosa may be red and enlarged. Symptoms may last as long as 4 to 5 weeks. In some patients, involvement of the major salivary glands does not occur, making diagnosis more difficult. In these cases the diagnosis is made by detecting viral-specific antibodies in the blood or by recovering the mumps virus from the urine.

TREATMENT

No antiviral agents are available for the treatment of mumps. Patients are treated symptomatically with analgesics, bed rest, and a bland diet. As with measles and rubella, mumps is managed through aggressive vaccination programs for young children in an attempt to reduce the presence of the virus in the population.

HUMAN PAPILLOMA VIRUSES

The human papilloma viruses (HPVs) are part of the papovavirus family. They are DNA (double-stranded) viruses with a spheric virion measuring 50 nm in diameter. Structurally they consist of a nucleocapsid without an outer envelope. Based on analysis by DNA sequencing, nearly 100 HPV subtypes have been identified to date. These have been grouped according to the specific diseases in which the clusters of subtypes are found. HPV exhibits tropism for epithelial cells and is found in normal oral mucosa, presumably in a latent stage, and in many other benign, premalignant, and malignant lesions. Of the different subtypes of HPV, approximately 24 specifically infect genital and oral mucosa. Within the oral cavity the benign clinical entities that contain one or more of the HPV subtypes are squamous papilloma (HPV 6 and 11); verruca vulgaris (HPV 2 and 4); and condyloma acuminatum (HPV 6 and 11). Inverted papilloma (HPV 6, 11, and 16) is sometimes found within the nasal passages and sinuses.

Certain HPV subtypes designated as *high-risk subtypes* are strongly associated with some dysplastic and neoplastic epithelial lesions. HPV 16, 18, and 31 have been found in 95% of cervical and anogenital cancers.

HPVs are ubiquitous human pathogens that cause a wide variety of benign and premalignant epithelial tumors. Mucosal HPVs are most frequently sexually transmitted and, with an incidence roughly twice that of HSV infection, are considered one of the most common sexually transmitted diseases throughout the world. A genital high-risk subset of HPV is highly associated with the development of genital cancers, including cervical carcinoma.

The absence of a simple monolayer cell culture system for analysis and propagation of the virus has substantially retarded progress in the development of diagnostic and therapeutic strategies for HPV infection. In spite of these difficulties, great progress has been made in the elucidation of the molecular controls of virus gene expression, replication, and pathogenesis. With the continued development of this knowledge base, great potential exists for the development of improved diagnostic and prognostic tests, prophylactic and therapeutic vaccines, and the development of antiviral agents.

Mucosal lesions containing one or more HPV subtype appear clinically as single or multiple areas of thickened epithelium, often with a papillary surface. The presence of fine hairlike surface projections (papillary) is common in some lesions. Lesions may be raised and exhibit a thin stalk (pedunculated) or flat and diffuse on a broad base (sessile). Most are whitish, but the flatter, broad-based lesions may be reddish or exhibit the pinkish color of normal oral mucosa.

Squamous Papilloma

SQUAMOUS PAPILLOMA: A papillary focal epithelial hyperplasia common in the posterior aspect of the mouth, containing koilocytic cells and HPV 6 and 11.

Squamous papillomas are the most common benign neoplasms of oral epithelium. They are present throughout the mouth in patients of all ages; however, a higher incidence is found on the soft palate, faucial pillars, and uvular areas. They are usually solitary lesions; however, multiple lesions can occasionally occur in young patients. Koilocytes may or may not be evident in the epithelium. Although these lesions do not appear to contain HPV genomic material, *in situ* DNA hybridization research indicates that HPV subtypes 6 and 11 are usually detectable.

Verruca Vulgaris

VERRUCA VULGARIS: A papillary focal epithelial hyperplasia commonly containing koilocytic cells and HPV 2 or 6; usually occurs on the hands and in the anterior aspect of the mouths of children.

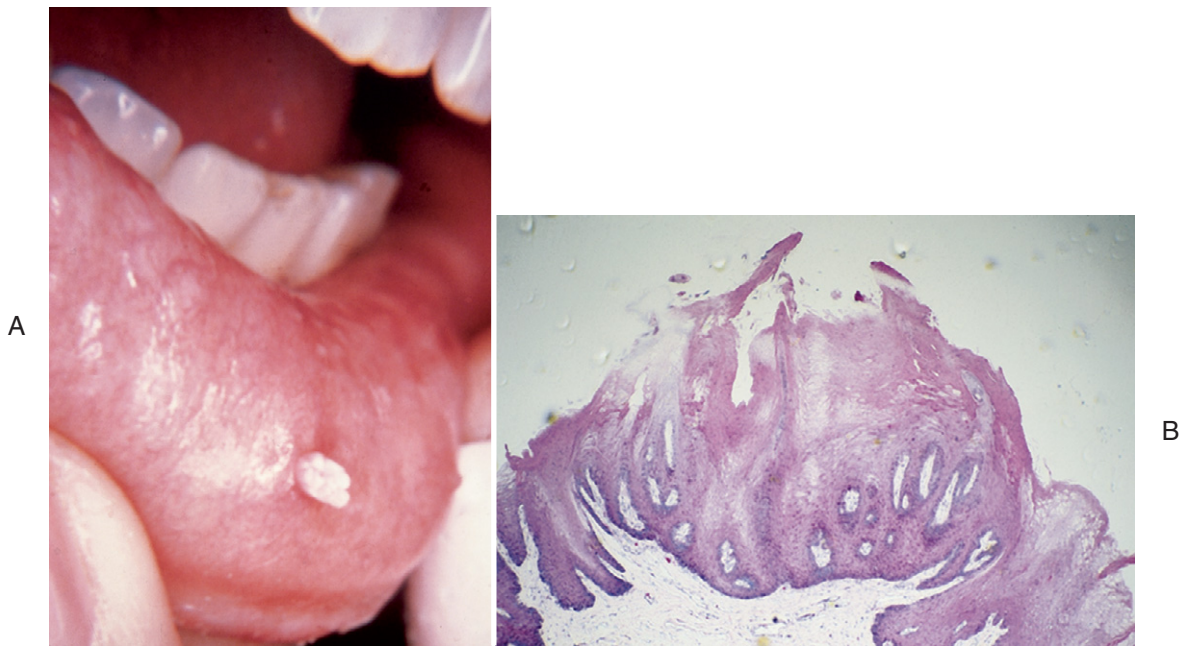
Verruca vulgaris is generally known as a *wart* when it occurs on skin. It is commonly found on the hands and fingers of children. The virus contained within the epithelial cells can be spread by autoinoculation; lesions spread from the fingers to other sites, particularly the lips, hard palate, and gingiva. HPV subtypes 2 and 6 are present in nearly all of these lesions.

CLINICAL FEATURES

The lesions are exophytic, keratinized, sessile papules or nodules with "warty" (cauliflower) surfaces (Figure 7-14, A). Lesions measure 2 to 5 mm in diameter, although much larger lesions occasionally occur. The skin and oral mucosal lesions are similar in appearance, except that the oral lesions are usually white and the skin lesions are usually grayish brown. This difference in coloration between skin and mucosal lesions is primarily related to the moist environment of the mouth as compared with the dry environment on the skin surface.

HISTOPATHOLOGY

Lesions consist of papillary epithelial proliferation in the form of multiple fingerlike projections exhibiting hyperkeratosis and a prominent granular cell layer. Mild degrees of basilar hyperplasia and radially oriented rete pegs are present (Figure 7-14, B). Variable numbers of superficial epithelial cells with shrunken nuclei and perinuclear clearing (koilocytosis), which indicates HPV infection, are seen. The connective tissue exhibits dilated vascular channels and some variable numbers of chronic

**FIGURE 7-14**

Verruca vulgaris. **A**, Clinical appearance of mucosal lesions are white, solitary, and exophytic, with a stalk and a papillary (wart) surface. **B**, Low-power photomicrograph reveals extensive keratin production, acanthosis, and radially oriented rete pegs.

inflammatory cells. Lesions display viral particles, both ultrastructurally and immunohistochemically.

TREATMENT

Some lesions will regress spontaneously. Those that persist should be excised surgically. Recurrence of intraoral lesions may occur but is uncommon.

Condyloma Acuminatum

CONDYLOMA ACUMINATUM: Multiple papillary or sessile focal areas of epithelial hyperplasia of the genital and oral mucosa that contain koilocytes, HPV-6 or HPV-11, and is difficult to eradicate.

Condyloma acuminatum, commonly termed *genital* or *venereal wart*, occurs most commonly on the genitalia; however, oral lesions are common. The lesions are caused by the HPV (usually HPV-6 and HPV-11). Although many oral lesions are acquired through oral-genital sexual contact, some cases are transmitted through nonsexual contact or autoinoculation from genital lesions. Oral lesions in young children can be particularly problematic, because sexual abuse may be involved.

CLINICAL FEATURES

Condyloma acuminatum presents as solitary or multiple, pinkish, sessile papules or plaques with pebbled surfaces (Figure 7-15, A) or as pedunculated papillary

lesions (Figure 7-15, B). Oral lesions occur predominantly on the nonkeratinized mucosa of the lips, floor of the mouth, lateral and ventral surfaces of the tongue, buccal mucosa, and soft palate. Gingival lesions do occur; however, they are uncommon.

HISTOPATHOLOGY

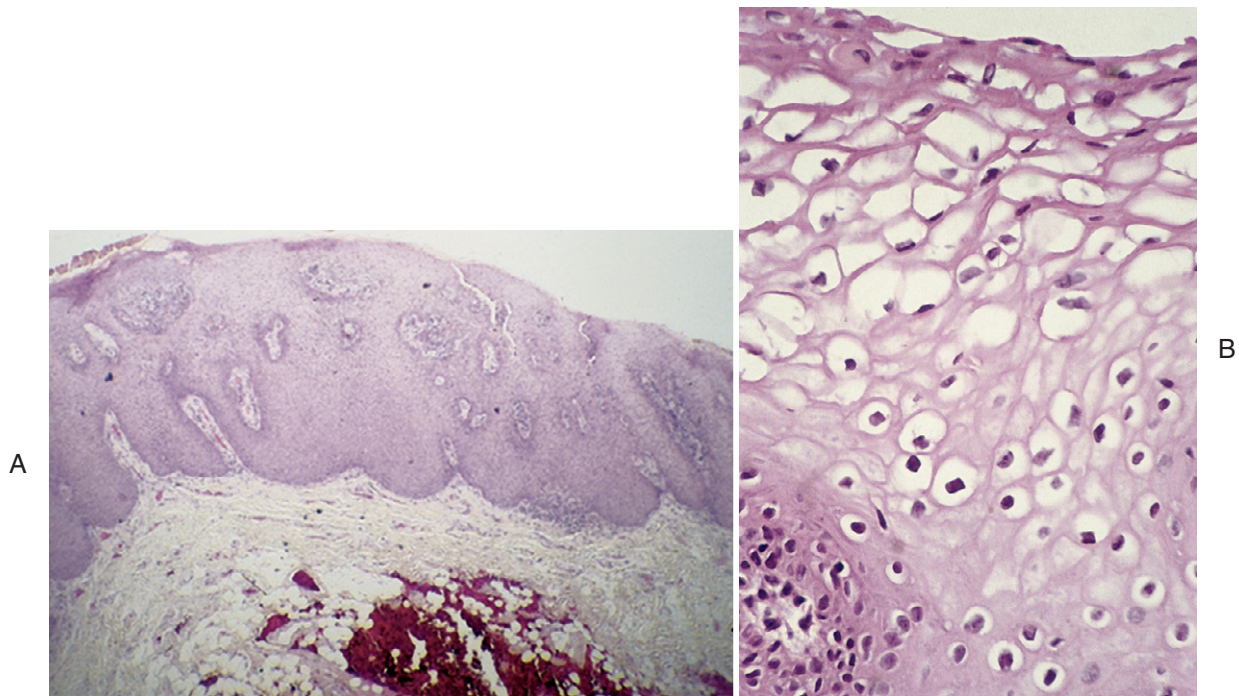
Lesions are characterized by an epithelial proliferation exhibiting broad, blunt, or rounded surfaces. The epithelium may be either nonkeratinized or parakeratinized. Often lesions will exhibit a marked degree of acanthosis or pseudoepitheliomatous hyperplasia, or both, with a moderate to marked degree of basilar hyperplasia (Figure 7-16, A). Increased numbers of mitotic figures are usually present in the basilar region. The spinous layer of the epithelium is generally hypercellular with a variable degree of nuclear pleomorphism. A characteristic feature of condyloma acuminatum is the presence of variable numbers of superficial spinous cells exhibiting shrunken nuclei with perinuclear clear zones (koilocytes), indicative of an HPV infection (Figure 7-16, B). The connective tissue is usually edematous, exhibiting prominent vascular channels and a variable degree of chronic inflammation.

TREATMENT

A solitary, small condyloma is best treated by a simple excision that includes a narrow border of clinically normal mucosa around the base of the stalk. Multiple small

**FIGURE 7-15**

Condyloma acuminatum. **A**, Multiple sessile flat lesions with pebbly surfaces. **B**, Papillary lesions present in the left corner of lower lip.

**FIGURE 7-16**

Condyloma acuminatum. **A**, Low-power photomicrograph of a common flat lesion exhibiting extensive epithelial hyperplasia with acanthosis and fusion and blunting of rete pegs. **B**, Medium-power photomicrograph of spinous cell layer containing clear cells with shrunken nuclei and perinuclear clear zones (koilocytes).

isolated lesions are similarly treated. Large fleshy lesions are more difficult to treat. Surgery or removal by cryotherapy or laser is the preferred treatment modality for these lesions. Although topical podophyllin is used for treating genital lesions, it is hazardous for treating

oral lesions and therefore contraindicated. A topically applied interferon inducer, imiquimod, has also been used with some success. Recurrence of treated lesions is common. Barrier methods to prevent sexually transmitted subtypes are effective for anogenital lesions.

Focal Epithelial Hyperplasia

FOCAL EPITHELIAL HYPERPLASIA: Multiple papillary or sessile areas of epithelial hyperplasia of the oral mucosa in young patients of specific population isolates that frequently regress spontaneously; the epithelium is extensively thickened and contains koilocytes, HPV-13, and HPV-32.

Focal epithelial hyperplasia, commonly known as *Heck disease*, is a condition found primarily in isolated groups of native Indians of North and Central America and Brazil, northern native peoples, and other groups in Europe and Africa. The lesions are usually multiple and often involve the gingiva and buccal and labial mucosa of the mouth (Figure 7-17, A). Lesions are sessile and may be pink or white. Although most lesions occur in children, they can also be found in older patients. Recently they have been found in HIV-positive or otherwise immunosuppressed patients. In children most of the lesions regress spontaneously. If lesions persist they can be surgically excised. The lesions contain abundant HPV-13 and HPV-32.

HISTOPATHOLOGY

Greatly thickened layers of parakeratin and extensive acanthosis characterize the surface of focal epithelial hyperplasia. Epithelial cells of the upper spinous layer display enlarged nuclei and vacuolated clear cytoplasm (koilocytes) indicative of an HPV infection. The basal cell layer exhibits increased mitotic activity. Cells with an unusual arrangement of the nuclear material resembling abnormal mitotic figures are a frequent finding within the spinous cell layer. These have been referred to as *mitosoid cells* or *bodies* (Figure 7-17, B). The underlying connective tissue is usually loose and well vas-

cularized, exhibiting a variable infiltrate of lymphocytes.

TREATMENT

Those lesions that do not regress spontaneously can be surgically excised. Until the diagnosis has been firmly established for individual patients, lesions should be surgically excised and submitted to a laboratory for a definitive diagnosis. Topical treatment with beta interferon has been found to be an effective alternative for some patients.

RETROVIRUSES

The members of the retrovirus family have been extensively studied for some time because of their known oncogenic potential in animals. The first retrovirus that exhibited this potential was the Rous sarcoma virus. Once injected into chickens, it rapidly produced sarcomas. In 1981 during the search for the causative agent of AIDS, another retrovirus, the human T-lymphotropic virus 1 (HTLV-1), was found to be the causative agent of T-cell leukemia in humans. Two years later a retrovirus was isolated from a patient with AIDS and named the human immunodeficiency virus. The virus became known as HIV-1; a less common variant of the virus, HIV-2, has since been isolated from patients with a similar disorder in regions of West Africa.

Human Immunodeficiency Virus

HIV exhibits tropism for T lymphocytes, macrophages, and certain nerve cells. The viral envelope contains specific surface glycoproteins, notably gp120 and gp41 (Figure 7-18, A), which bind with both the primary

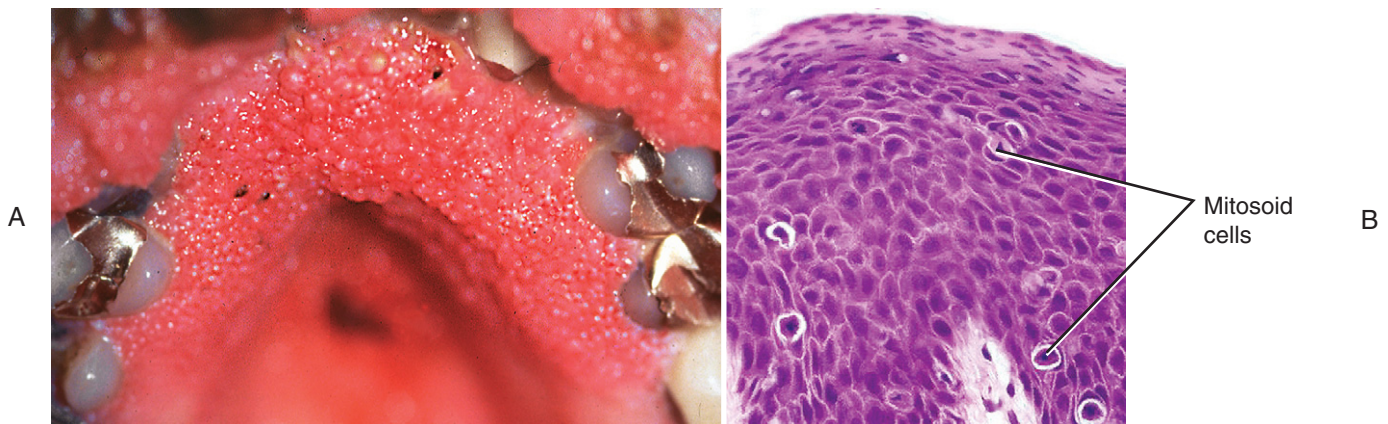


FIGURE 7-17

Focal epithelial hyperplasia. **A**, Multiple sessile and papillary lesions of the anterior gingiva and labial mucosa of an adult. **B**, Spinous layer epithelial cells with unusual arrangement of the nuclear material resembling abnormal mitotic figures (mitosoid cells).

CD4 receptor and the CCR5 or CXCR4 co-receptors on the surface of T-lymphocyte helper cells or macrophages. Successful binding allows the contents of the viral core to enter the cytoplasm of the host cell, leaving the viral envelope behind. The core contains enzymatic proteins p64, p34, p10, and p6 that are necessary for the virus to use the constituents of the host cell for replication. Once within the cell cytoplasm the RNA of the viral nucleocapsid uses its viral enzyme **reverse transcriptase** to synthesize strands of viral DNA, using the viral RNA as the template. The newly formed viral DNA enters the host nucleus and becomes spliced into the genome of the host cell using another viral enzyme, *integrase*. The integrated viral genome is now able to maintain a dormant or latent state. Periodically this integrated proviral DNA is transcribed to RNA, where it directs the metabolic activity of the host cell to synthesize more HIV RNA genome. This RNA genome encodes the retroviral structural proteins *gag*, *pol*, and *env*; as well as the proteins *nef*, *tat*, and *vpu* that regulate viral replication and suppress the immune system (Figure 7-18, B). The level of metabolic and mitotic activity of the host CD4 cell is believed to be a factor in the rate at which the disease progresses in individual patients. In patients with lower levels of CD4 cell stimulation,

there may be a prolonged period of latency before the devastating clinical effects of an HIV infection are apparent. In patients with active or chronic infections that heightened the activity level of the CD4 cells, a noticeable increase is seen in the rate in which the disease progresses. This is believed to result from the infectious agents acting as mitogenic stimulators of the CD4 cells that have been previously genetically altered by the retrovirus. This results in the production of overwhelming amounts of viral protein that leads to the rapid and premature death of the stimulated CD4 immune cell. To sustain adequate immune function, a helper and suppressor T-cell ratio of 2:1 is required. During the latency-like state, which may last for 3 to 8 years, a slow but progressive functional deterioration of the T4:T8 cell ratio occurs until the immune system can no longer prevent normal commensal or latent organisms from becoming potent infective agents. Normally patients have 800 to 1200 such T cells per μL . With progressive CD4 lymphocyte depletion, immunosuppression becomes increasingly more severe with the emergence of pre-AIDS opportunistic infection. Once the CD4 lymphocyte count falls below 200 cells per μL and the ratio of helper and suppressor cells is reversed, a diagnosis of AIDS is made.

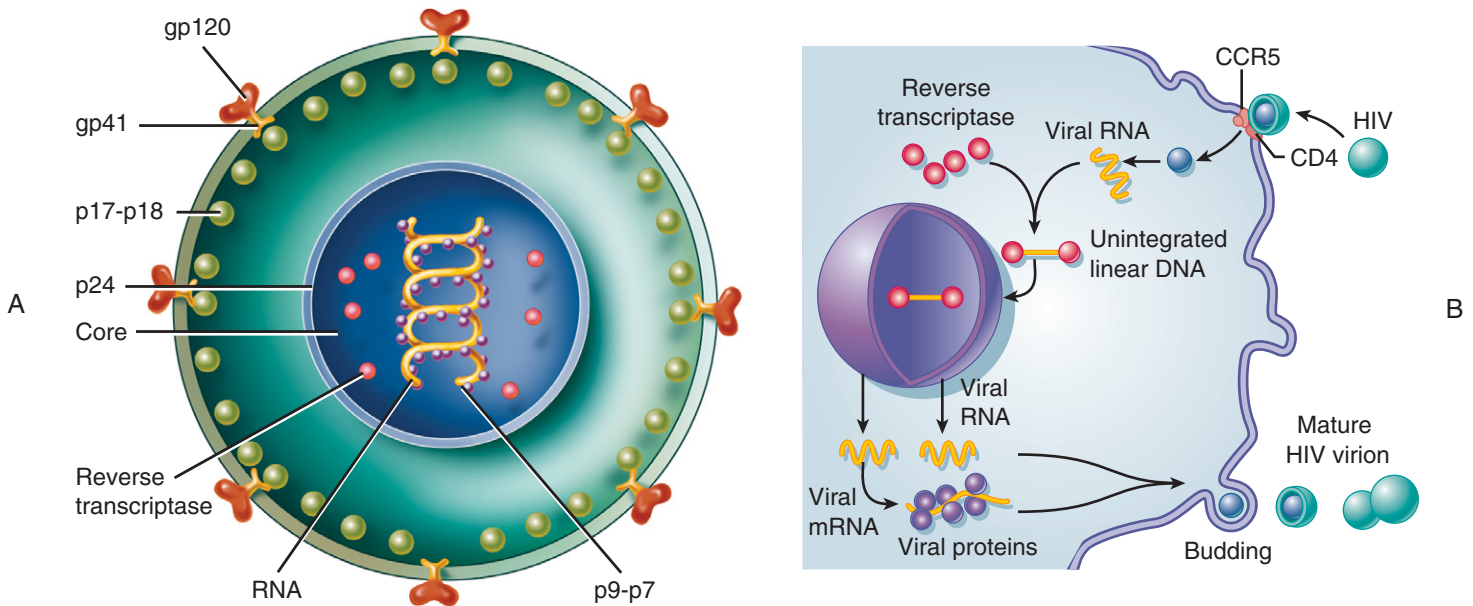


FIGURE 7-18

Human immunodeficiency virus. A, A retrovirus with essential envelope glycoproteins, core enzymatic proteins, and RNA chromatin. **B,** Process of replication of human immunodeficiency virus (HIV) retrovirus. The virus attaches to a target cell, usually a lymphocyte with a surface CD4 receptor and either a CCR5 or a CXCR4 co-receptor. Cytoplasmic reverse transcriptase changes virus' RNA to DNA that becomes integrated into the nuclear genome directing the cell to produce cytoplasmic viral RNA and other viral proteins sufficient to replicate HIV.

The drastic reduction in total lymphocytes, particularly the CD4 lymphocytes, results in the loss of production of the noncellular components of the defense system of the body. These include the essential lymphokine factors such as interleukin 2 (IL2), interferon (IF), the macrophage activating factor (MAF), and the factors that stimulate the production of natural killer (NK) cells. Additionally a gammaglobulinemia, which is often associated with a compensatory increase in the number of B cells, may occur.

CLINICAL FEATURES

Patients with HIV infection progress through clinical stages that vary extensively among individuals. During this time the *viral load* (measured as antibodies to the virus) increases while the CD4 count decreases (Figure 7-19). Five stages can be identified: (1) window, (2) seroconversion, (3) asymptomatic, (4) symptomatic, and (5) AIDS.

Window Stage

After initial contact with HIV, commonly a 2 to 12 week delay is seen before antibodies to the virus are detectable in the blood using the ELISA technique. During this period, patients are unaware of their status; testing will often yield a false negative. If suspicion is high that an infection has taken place, a more specific test that targets actual specific HIV antigens, known as the *Western blot*

technique, is usually confirmatory of the patient's status if sufficient viral particles are present in the blood.

Seroconversion Stage

Over the ensuing weeks as antibodies and virus appear in the blood in greater numbers, patients will experience noticeable malaise, lethargy, mild temperature elevation, headache, arthralgia, myalgia, chronic cough, and possibly a skin rash. These symptoms are similar to those of flu or a mild form of infectious mononucleosis. This period usually lasts between 2 and 4 weeks.

Asymptomatic Stage

This phase consists of a prolonged period of latency, with few if any symptoms that may last for 6 months in infants and 10 to 20 years in adults. Although the level of HIV viremia achieved during the first year after initial infection does not correlate with the rate of progression to clinical AIDS and survival, the level of viremia present at the 1 year mark ("set point") and during the following prolonged latency period are significant. The lower the levels of the viral load during this period, the longer the survival rate. Viral loads less than 4500/ml at the "set point" and during the latest period have resulted in survival well beyond 10 years, whereas loads greater than 36,000/ml have greatly shortened survival. With the advent of numerous drugs or combinations of drugs, such as the highly active antiretroviral therapy (HAART) protocol, to inhibit viral reverse transcriptase and enzyme proteases, viral loads or viremia during latency have been significantly reduced. With the continued use of these intervention therapies, pre-AIDS states and eventual survival rates are expected to become significantly prolonged for patients who are able to tolerate the considerable drug side effects and complications. During this stage, patients may initially have no symptoms other than the gradual development of chronic lymphadenopathy.

Symptomatic Stage

Progression to the symptomatic stage varies extensively and is dependent on an individual decline in CD4+ T cell count. Some or all of the following insidious symptoms of pre-AIDS gradually appear:

- Night sweats, malaise, fever
- Weight loss
- Memory loss, mild dementia
- Chronic infections
- Generalized lymphadenopathy
- Diarrhea

AIDS Stage

Once an HIV-positive patient's CD4+ lymphocyte count falls below 200/ μ l, one or more of the following severe and disabling symptoms appear, or both happen, the patient is classified as having AIDS:

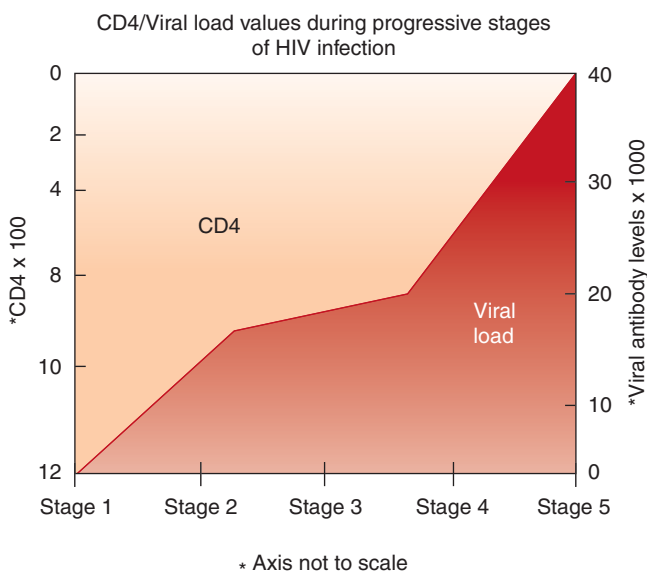


FIGURE 7-19

Correlation of reduction in CD4 blood levels and increase in "viral load" with progression of stages (see text) of human immunodeficiency virus (HIV) infection from initial contact (stage 1) through to acquired immunodeficiency syndrome (AIDS, stage 5). For conceptual purposes only, actual values differ extensively between individuals.

- *Pneumocystis carinii* pneumonia
- Bacterial pneumonia
- Cryptosporidiosis
- Toxoplasmosis
- Cerebral meningitis
- Kaposi sarcoma
- Non-Hodgkin lymphoma (NHL)
- Generalized herpes simplex, varicella-zoster infections
- CMV retinitis, pneumonia, colitis
- Candidiasis, cryptococcosis, coccidioidosis, histoplasmosis, or other deep mycotic infections
- *Mycobacterium avium-intracellulare* infections

The oral manifestations of HIV-infected patients are multiple and varied and are occasionally the first sign that patients harbor the virus. The lesions that develop are the result of an inadequate immune surveillance system and consist of either opportunistic infections or neoplasms. Box 7-1 lists the oral lesions found in HIV-positive patients in the symptomatic stage or pre-AIDS stage when CD4+ lymphocyte counts are reduced and range from 800 to 200 cells per μ l.

The more common oral conditions that may occur in patients with AIDS are listed in Box 7-2. Occurring less frequently within the oral cavity of AIDS patients are one or more of the lesions listed in Box 7-3.

BOX 7-1

Oral Lesions of HIV-Positive Pre-AIDS Patients

Hairy leukoplakia
Acute pseudomembranous candidiasis
Diffuse herpes simplex gingivostomatitis
Gingivitis/periodontitis
Acute nonspecific ulcers
Diffuse varicella-zoster lesions

BOX 7-2

Common Oral Lesions in Patients with AIDS

Candidiasis	Non-Hodgkin lymphoma
Intraoral	HIV gingivitis/periodontitis
Esophageal	Acute nonspecific ulcers
Hairy leukoplakia	Chronic ulcers
Diffuse herpes simplex gingivostomatitis	Cryptococcosis
Diffuse varicella-zoster lesions	Histoplasmosis
Kaposi sarcoma	Cytomegalovirus ulcer
	Herpes simplex infection

BOX 7-3

Infrequent Oral Conditions Found in Patients with AIDS

Atypical tuberculosis
Coccidioidomycosis
Molluscum contagiosum infection
Toxoplasmosis
Bacillary angiomatosis
Condyloma acuminatum
Enlarged parotid glands
Xerostomia
Squamous cell carcinoma

Hairy Leukoplakia

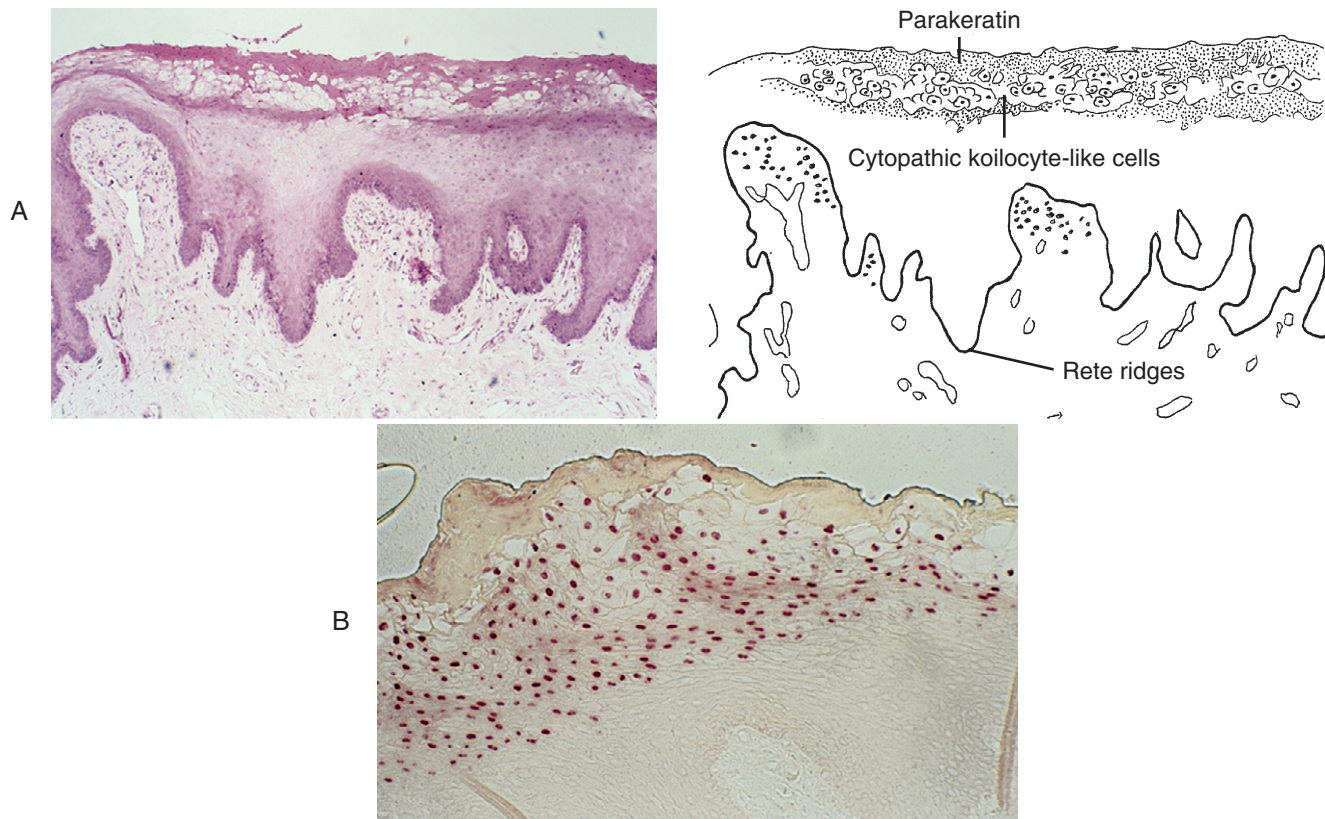
HAIRY LEUKOPLAKIA: *White patches of the lateral borders of the tongue that have a tendency for vertical linear folds found in latency stages of HIV-infected patients; the thickened epithelium contains an upper zone of clear cells (koilocytes), most of which contain EBV.*

Hairy leukoplakia is a white lesion located primarily on the lateral borders of the tongue and occasionally on the adjacent buccal mucosa. The lesion has a linear, folded appearance that was originally described as "hairlike" (Figure 7-20). It appears during the late latency stages of HIV infections and is considered a precursor of AIDS. Because other conditions can mimic hairy leukoplakia, it is important to remember that its clinical presence alone



FIGURE 7-20

Hairy leukoplakia. White lesions with vertical striations on the lateral surface of the tongue; common in human immunodeficiency virus-positive patients but occasionally found in patients with other causes of immunosuppression.

**FIGURE 7-21**

Hairy leukoplakia. **A**, Low-power photomicrograph of a lesion from the lateral surface of the tongue that exhibits characteristic hyperparakeratosis and acanthosis with a zone of vacuolated koilocyte-like cells. **B**, Presence of Epstein-Barr virus (EBV) in the upper layers of the epithelium as revealed by in situ hybridization.

is not indicative of an HIV-positive status. Histologic features of hairy leukoplakia include hyperparakeratosis and acanthosis with a zone of enlarged cells (koilocyte-like cells) in the upper region of the stratum spinosum (Figure 7-21, A). The koilocytotic cells usually contain the EBV as evidenced by immunohistochemistry or in situ hybridization (Figure 7-21, B). Because other causes of immunosuppression will also have these findings, the presence of the HIV antibody in the serum is necessary for a diagnosis of an HIV-positive status. Many of these lesions will also show superficial colonization by *Candida albicans*. The underlying connective tissue is usually free of an inflammatory reaction to the organisms, which is indicative of a diminished level of immunoreactivity.

Candidiasis

Persistent and refractory acute or chronic forms of *C. albicans* infection of the oral mucous membranes, in an otherwise healthy patient, is an important early indicator of impending deterioration of the immune system in HIV-positive patients. It is often associated with nasopharyngeal, esophageal, epiglottic, and laryngeal can-

didiasis (Figure 7-22). Other species of *Candida*, including *C. tropicalis*, *C. glabrata*, and *C. parapsilosis*, are commonly found in HIV-positive patients and may account for differences in their responses to treatment.

**FIGURE 7-22**

HIV candidiasis. Persistent acute pseudomembranous candidiasis on the palate.

Deep (Invasive) Fungal Infections

Although candidiasis is the most common infection in HIV-positive patients, infections by mycotic organisms capable of penetrating into the underlying connective tissue are occasionally encountered. The most common of these infections is histoplasmosis. It is characterized by mucosal ulceration or red granular swellings. The organisms are easily detectable in a biopsy specimen. Oral lesions are usually only a manifestation of a more widespread systemic infection.

Gingivitis and Periodontitis Associated with Human Immunodeficiency Virus Infection

Some HIV-positive patients will develop an atypical form of gingivitis and periodontitis. In those lesions in which the gingiva develops an unusually intense narrow zone of erythema of primarily the free gingiva, it is referred to as *linear gingival erythema* (LGE) (Figure 7-23). The distribution of the lesions is unique in that some teeth are spared, whereas others are severely affected (so-called "skip lesions"). In the severely immunocompromised (CD4 cells $<100/\mu\text{l}$), the condition can be rapidly progressive, moving quickly from gingivitis to periodontitis (Figure 7-24), and is unresponsive to the usual treatments. In some cases the gingivitis occurs as an atypical form of necrotizing ulcerative gingivitis (NUG), often superimposed on a rapidly progressive periodontitis. The periodontitis differs significantly from the usual type in that a rapid denuding of the gingival tissue commonly takes place, with resultant exposure of the alveolar bone; this has been termed *necrotizing ulcerative periodontitis* (NUP). Severe pain, odor, and spontaneous bleeding accompany the condition, features uncommon in periodontal disease of non-HIV patients.



FIGURE 7-23
HIV linear gingival erythema. Atypical, intensely erythematous gingival inflammation involving several teeth with uninvolved adjacent gingiva.



FIGURE 7-24
HIV necrotizing ulcerative periodontitis. Focal areas of an advanced gingival recession and an erythematous gingiva, with features suggestive of a superimposed acute necrotizing ulcerative gingivitis.

Acute Nonspecific Ulcers

The oral ulcers in HIV-positive patients resemble larger and deeper versions of aphthous ulcers (Figure 7-25). They are crateriform, with a large erythematous halo. The edges are often sharp or thickened. The center will quickly expose bone or penetrate muscle unless it is treated. Treatment involves tissue examination to determine if the lesion is the result of a specific infection such as herpes, CMV, or an invasive fungus. If no specific infectious organism is identified, as is often the case, steroid therapy is usually effective.



FIGURE 7-25
Acute nonspecific ulcer. Deep crateriform ulcer with rolled borders and no identifiable causative factor that is penetrating the underlying muscle in a patient who is HIV positive.

Kaposi Sarcoma

KAPOSI SARCOMA: Macular or nodular vascular lesions occurring singularly or in multiples on the mucosa and skin of HIV-infected patients; lesions consist of proliferating atypical endothelial cells and are indicative that the patient has AIDS.

Oral lesions of Kaposi sarcoma eventually occur in 10% to 20% of HIV-positive male patients and are more common in those patients who acquire the virus through sexual transmission rather than IV drug abuse. HHV-8 has been strongly associated with the development of Kaposi sarcoma in HIV-positive patients, although its exact role has not been clearly defined. The lesions are reddish to deep purple and may be macular or nodular (Figure 7-26, A and B). The predominant locations within the oral cavity are the hard and soft palates, followed by the maxillary gingiva (Figure 7-26, C). The early macular lesions are difficult to differentiate from a persistent hematoma, whereas the early nodular lesions resemble pyogenic granuloma. On the gingiva, large lesions will often interfere with mastication. Large palatal lesions interfere with speech and may undergo spontaneous bleeding. Oral lesions may or may not be accompanied by skin lesions.

The histopathology of Kaposi sarcoma is not always distinctive in the early lesions, because the tissue may resemble other benign vascular lesions such as capillary hemangioma or pyogenic granuloma. The more mature lesions exhibit a proliferation of hyperchromatic spindle-shaped or oval endothelial cells arranged in an irregular vascular pattern (Figure 7-27, A). In some lesions distinct vascular spaces are present that have plump and rounded endothelial cells projecting into the vascular lumina (Figure 7-27, B); in other lesions only occasional slitlike spaces with a few distinct vessels are found. Extravasated red blood cells and hemosiderin deposits are characteristically present.

Patients with lesions and few other outward signs of their HIV status are often anxious to have them removed. Diagnosis should be confirmed by biopsy, because hematomas, pyogenic granulomas, and other vascular lesions may have similar clinical appearances. Lesions have been treated by radiotherapy; surgery; and intralesional injections of adriamycin, vinblastine, vincristine, bleomycin, and other antimetabolites.

Small lesions have been eliminated with sclerosing agents. Some preliminary research suggests that removing

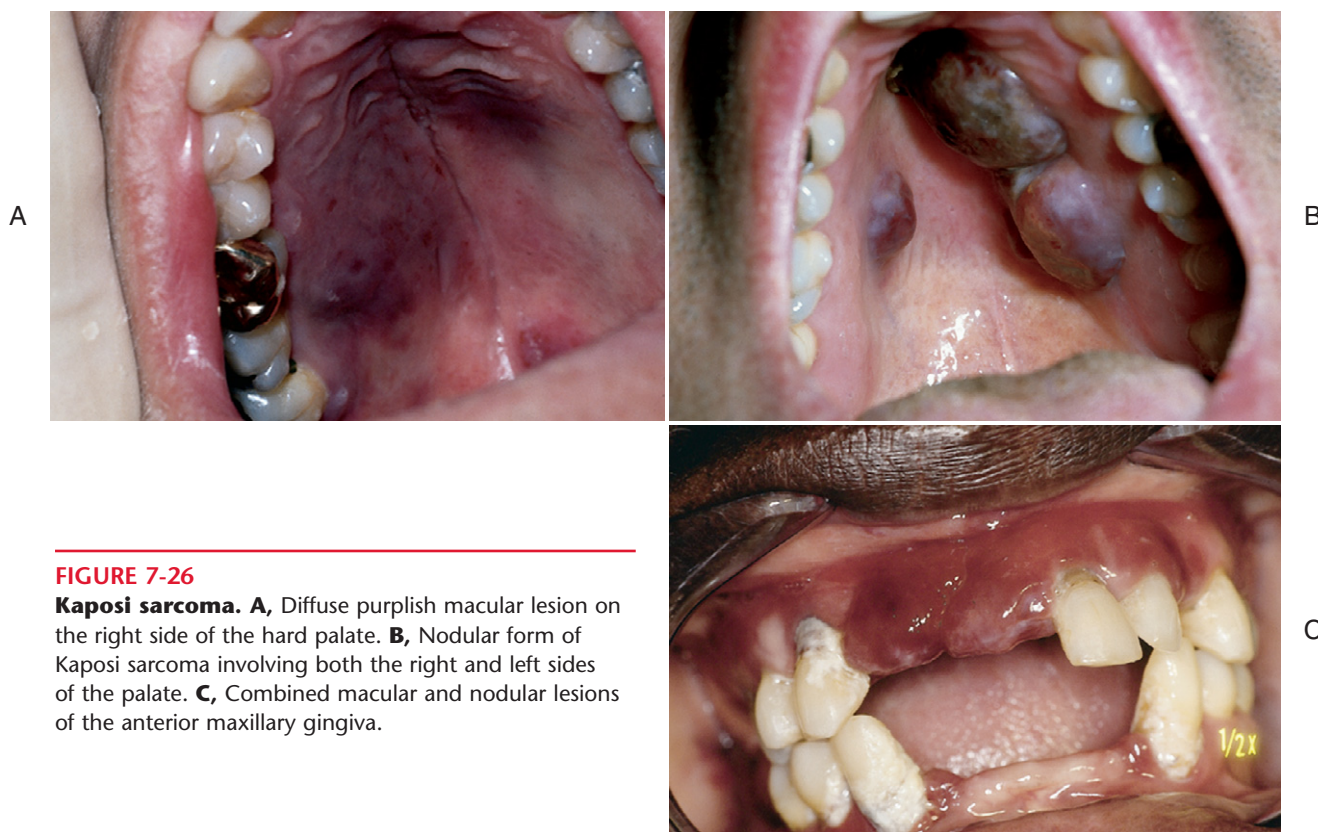
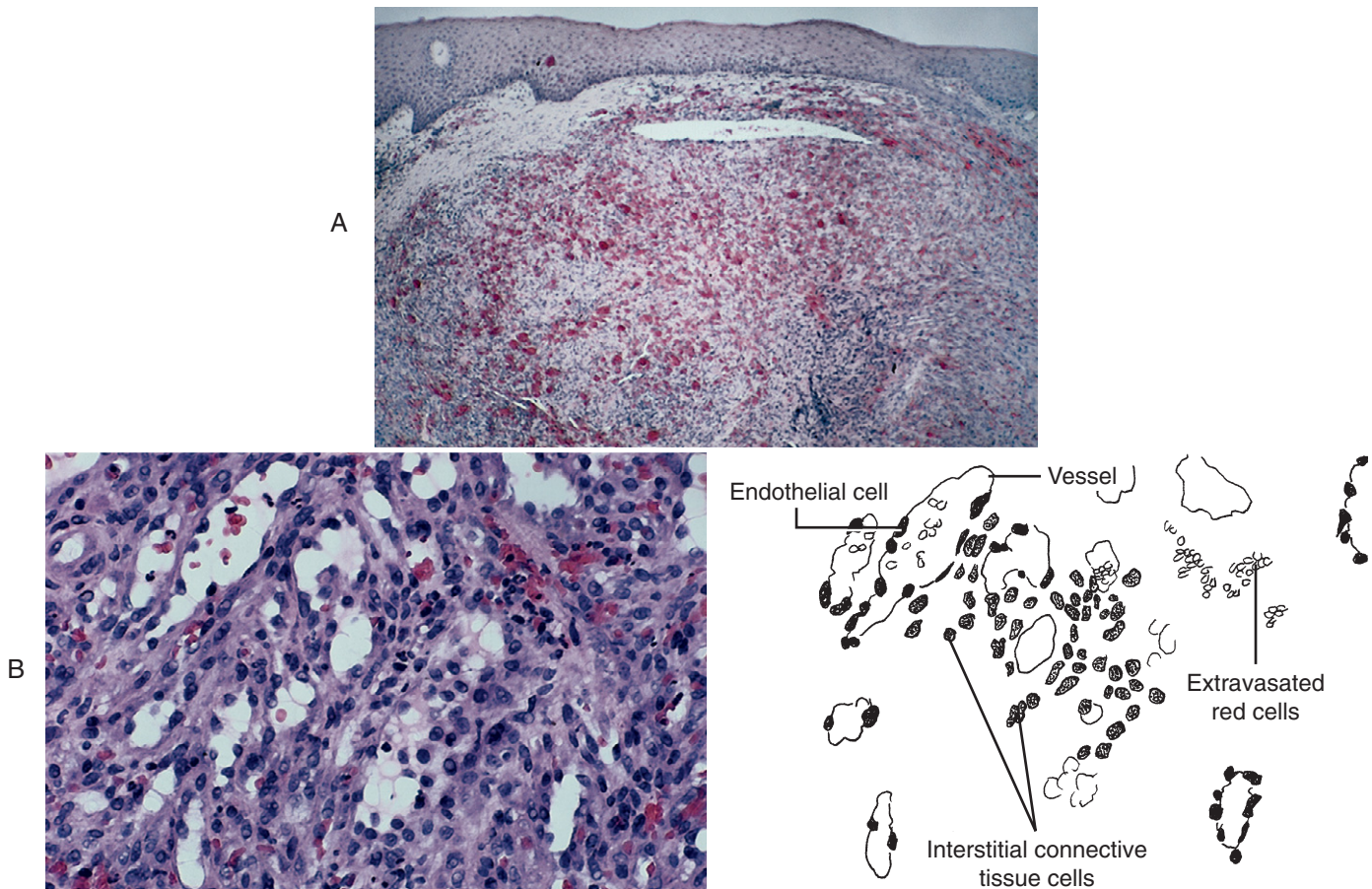


FIGURE 7-26

Kaposi sarcoma. **A**, Diffuse purplish macular lesion on the right side of the hard palate. **B**, Nodular form of Kaposi sarcoma involving both the right and left sides of the palate. **C**, Combined macular and nodular lesions of the anterior maxillary gingiva.

**FIGURE 7-27**

Kaposi sarcoma. **A**, Low-power photomicrograph reveals a circumscribed submucosal nodule of highly vascular tissue with abundant extravasated red blood cells. **B**, High-power photomicrograph revealing abnormally shaped and incompletely formed blood vessels composed of rounded, plump endothelial cells.

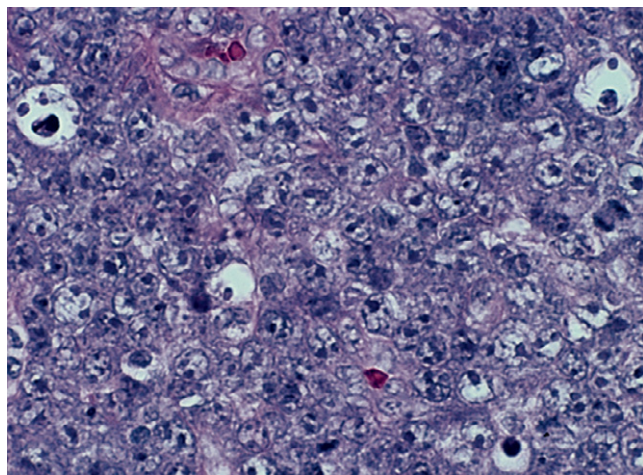
small, early lesions may prevent the development of additional ones.

Non-Hodgkin Lymphoma

The lymphomas seen in HIV-positive patients are primarily the B-cell type of lesions. Although the lesions are not common within the oral cavity, they have been reported in nearly all anatomic locations. They are characterized by their rapid appearance and growth, which quickly undergoes ulceration. The borders are raised, rolled, and indurated (Figure 7-28). The histopathology reveals a uniform distribution of a single cell type, usually consisting of the less mature forms of B cells and immunoblasts (Figure 7-29). Many cells exhibit features in common with Burkitt lymphoma. The presence of NHL in HIV-positive patients is a sign of a poor prognosis, with few patients surviving for 2 years.

**FIGURE 7-28**

Non-Hodgkin lymphoma. Rapidly enlarging lesion with central ulceration on the dorsal side of the tongue.

**FIGURE 7-29**

Non-Hodgkin lymphoma. High-power photomicrograph demonstrating densely packed large immature lymphocytes and immunoblasts in a lymphoma in a patient who is HIV positive.

Viral Infections

The viral infections in HIV-positive patients are usually exacerbations of previous latent infections. In these patients the reactivated form does not remain localized and transient as occurs in nonimmunocompromised individuals. The recurrences more closely resemble primary infections, except that the viral infections are of an indefinite duration and capable of causing the death of the patient if they are not promptly and adequately treated. The viral infections usually found are herpes simplex and varicella, which appear as multiple diffuse ulcers that are larger and deeper than usual. CMV also occurs and is believed to be responsible for the bilateral swelling of the parotid glands and the reduction in salivary flow, which results in xerostomia. CMV is also found in deep focal ulcers and is thought to be responsible, along with EBV, for the generalized lymphadenopathy. EBV has been found in hairy leukoplakia and is thought to be the causative agent for that lesion. HPV infections are common in HIV-positive patients and are responsible for condyloma acuminatum and multifocal papular lesions resembling those seen in focal epithelial hyperplasia (Heck disease).

Pediatric Human Immunodeficiency Virus

Orofacial lesions commonly associated with pediatric HIV infection include candidiasis, herpes simplex infection, linear gingival erythema, parotid enlargement, and aphthous ulcers. In contrast, Kaposi sarcoma, NHL, and oral hairy leukoplakia are rare.

BACTERIAL INFECTIONS

STREPTOCOCCUS

The streptococci are a large group of gram-positive organisms, mostly facultative anaerobes that grow in pairs or short chains. They are classified according to the specific clinical diseases they cause, their serologic properties, hemolytic potential, and metabolic and biochemical properties. Two members of streptococci are of particular importance within the oral cavity: (1) *Streptococcus pyogenes*, a beta-hemolytic streptococcus responsible for pharyngitis, tonsillitis, impetigo, and some atypical forms of mucositis and gingivitis, and (2) *Streptococcus viridans*, an alpha nonhemolytic streptococcus that is a normal inhabitant of the oral cavity and is of importance in the pathogenesis of dental caries and bacterial endocarditis.

Pharyngitis and Tonsillitis

Pharyngitis and tonsillitis, also referred to as *strep throat*, is an acute condition caused by a beta hemolytic streptococcus. It occurs primarily in young patients who are 5 to 15 years of age. It is spread by the inhalation of infected droplets present in crowded conditions. Symptoms of infection occur 2 to 4 days after contact and may include a sudden onset of elevated temperature, throat soreness, chills, malaise, cervical lymphadenopathy, and headache. Within a few days, petechiae may occur on the soft palate. All the oral mucous membranes may be erythematous and uncomfortable. Differentiation from the more common viral pharyngitis is required before treatment.

Scarlet Fever

Scarlet fever occurs when in addition to pharyngitis and tonsillitis, a rash occurs over the upper trunk and spreads to involve the extremities. The rash is composed of numerous minute red papules, giving the skin a roughened feel and appearance. The rash is the result of liberated erythrogenic toxins of beta-hemolytic streptococci becoming systemically disseminated in hypersensitive individuals. The oral cavity is often affected and exhibits generalized edema, elongation of the uvula, and diffuse petechiae. The dorsal surface of the tongue becomes whitened, and the fungiform papillae become erythematous and enlarged, appearing as small red papules against a white background. This appearance of the tongue has been referred to as *strawberry tongue*.

The skin rash lasts about 1 week and is followed by a period of desquamation. The development of acute glomerulonephritis and rheumatic fever is of greatest concern. Most patients recover from glomerulonephritis, but rheumatic fever may permanently damage the

heart valves. This predisposes the damaged valves to recurring infections during subsequent transit bacteremias. The chronic condition of recurring infections of the heart valves, primarily the mitral valve, is termed *subacute bacterial endocarditis* and is of great concern in the practice of dentistry. Patients with this condition are required to have prophylactic premedication with antibiotics before receiving invasive dental treatments.

Impetigo

IMPETIGO: Acute pustular eruptions of the perioral skin of children usually with inadequate perioral hygiene, in which *Streptococcus pyogenes* and *Staphylococcus aureus* are the most common pathogens.

Impetigo is the common name given to an acute pustular eruption of the perioral skin (Figure 7-30) in which *S. pyogenes* and *S. aureus* are the most commonly found pathogens. It is seen mostly in younger children and tends to occur in the warmer months and in tropical climates. It is closely associated with neglected personal hygiene. Lesions start as red papules that become pustular; when scratched they coalesce or spread the bacteria to other parts of the face in a linear or excoriated pattern. In some instances the fingernail beds also become infected. The clinical similarity between impetigo and perioral primary or recurrent herpes infections and allergic stomatitis can sometimes pose a diagnostic problem. Cultures from smears of lesional exudate are used to identify the causative organisms before treatment. Treatment consists of using both a topi-



FIGURE 7-30

Impetigo. Pustular and crusted perioral lesions commonly harboring *Streptococcus pyogenes* and *Staphylococcus aureus* pathogens in a young patient. (Courtesy Dr. S. Rovin and Dr. W. Sabes.)

cal ointment (e.g., mupirocin) and systemic antibiotics (e.g., dicloxacillin, cephalexin).

STAPHYLOCOCCUS

The members of the genus *Staphylococcus* are potent human pathogens that produce purulent exudate (pus) and cause a large array of diseases. The staphylococcus microorganism is a round, gram-positive, facultative anaerobic bacterium that grows in clusters. It is found on the skin and oronasopharyngeal surfaces of all humans. Members of this genus are the cause of most acute infections that occur after trauma and surgical procedures when aseptic technique is not rigidly followed. Staphylococci are capable of survival on nonhuman, dry surfaces for prolonged periods and are easily transferable. *S. aureus* is the best known strain of this genus; it is responsible for most common acute skin infections, such as folliculitis, furuncles, and carbuncles (boils). Fortunately the organisms are very susceptible to heat and chemical sterilization and can be controlled when proper aseptic protocols are followed.

Osteomyelitis

In the oral cavity, *S. aureus* is most commonly found in the acute forms of osteomyelitis, which can occur as a result of direct invasion through a break in the mucosa overlying the mandible and occasionally the maxilla or through hematologic spread from an adjacent or remote focus of infection. In the long bones, acute suppurative osteomyelitis is commonly found in younger patients who possess highly vascularized metaphyseal areas. Within the oral cavity, osteomyelitis usually occurs after dental caries and pulpitis progress to an intraosseous periapical infection. In these infections, *S. aureus* is the organism most commonly cultured from the exudate.

Treatment of deep infections of bone are often more difficult than soft tissue lesions, and they require drainage and debridement of necrotic tissue and prolonged high doses of penicillin or IV therapy. Resistant strains to many of the penicillin class of antibiotics are common.

MYCOBACTERIUM

Strains of the genus *Mycobacterium* are among the oldest and most treatment-resistant infections known to science. They are aerobic bacilli with a cell wall containing a high lipid component. This feature makes them resistant to medications that are in an aqueous solution. As aerobes they are able to survive and flourish in oxygenated environments such as the lungs. Their lipid cell wall also presents difficulty in detection with common histologic screening stains, such as Gram, Giemsa, and

H&E. Special acid-fast staining techniques are required for their detection in tissue sections. The common human infections by this genus include tuberculosis (*M. tuberculosis*) and leprosy (*M. leprae*), both of which have been the sources of numerous worldwide epidemics. With an increase in immunodeficiency syndromes, there has been a resurgence of cases of tuberculosis. The resurgence is complicated because of the emergence of new atypical strains, the most prevalent being *M. avium-intracellulare* that is particularly common in patients with AIDS.

Tuberculosis

TUBERCULOSIS: Chronic granulomatous infection of the lungs caused by *M. tuberculosis*, which is spread by aerosols; can occasionally have associated chronic oral ulcers, enlarged nasopharyngeal and cervical lymph nodes, or a combination.

Aerosols that usually enter the body through the lungs and lodge in the terminal alveoli spread tuberculosis. The bacilli are phagocytized and spread throughout the adjacent tissue by means of the motile macrophages present in the lungs. Within macrophages the microorganisms are protected by their lipid outer coat and are able to undergo rapid replication that eventually destroys the host cell, liberating large numbers of bacilli to invade new peripheral sites. The phagocytes spread the organisms to the regional lymph nodes and, if not halted by the immune system, to other organs such as the kidneys, bone marrow, and brain. Pivotal to the ability of the body to restrict the spread of the tuberculosis bacilli is its development of ample numbers of antibodies.

The presence of an antibody response in an infected patient can be detected by a positive skin reaction when challenged with fragments of the protein structure of the bacteria. This is referred to as the *purified protein derivative* (PPD) test and is widely used to identify those individuals who have contracted the organism, either recently or in the past.

CLINICAL FEATURES

Oral lesions have been found in 3.5% of patients with systemic tuberculosis. They are rarely seen unless the patient also has lung and possibly other systemic involvement. Patients who are immunocompromised have a much higher incidence of oral lesions. The lesions are commonly infected with atypical forms of the organisms such as *M. avium-intracellulare*.

The clinical appearance of an oral lesion is as a chronic ulcer with indurated borders (Figure 7-31) or as a swelling in the tonsils, other lymphoid-rich areas of the posterior aspect of the mouth and the nasopharynx, and regional cervical lymph nodes. Lesions may also be found intraosseously and may appear as chronic osteomyelitis; eventually the lesions drain and produce bony sequestra.



FIGURE 7-31

Tuberculosis. Chronic shallow nonhealing ulcer of the lateral surface of the tongue with associated induration. (Courtesy Dr. F.M. Lucatorto.)

HISTOPATHOLOGY

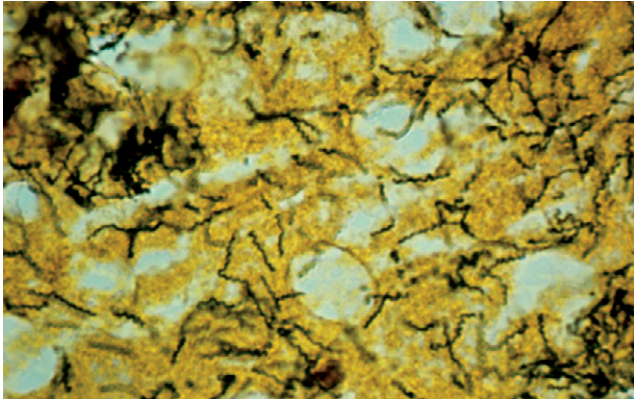
The microscopic appearance of the lesions within the oral cavity is the same as in the lungs, consisting of granulomas exhibiting a central necrotic focus surrounded by mononuclear cells and multinucleated Langhans giant cells. A mantle of lymphocytes and fibrous tissue usually surrounds the granuloma. Arrested lesions may show areas of dystrophic calcifications.

TREATMENT

Treatment of *M. tuberculosis* infections is difficult, because the lesions are resistant to common antibiotics. To maximize treatment efficacy and avoid resistant strain development, two antimycobacterial agents, isoniazid and rifampin, are combined (and augmented with pyrazinamide). Treatment extends over a period of 4 to 8 months.

TREPONEMA PALLIDUM

The microorganism *T. pallidum* is part of the order Spirochaetales, in which all members are thin, elongated, coiled, or helix-shaped structures that are gram negative. The bacteria of this order are commonly referred to as *spirochetes*. *T. pallidum* is the most common and is responsible for syphilis, the sexually transmitted disease that has been a major health problem for centuries. It occurs as a communicable disease in humans, because it does not survive well outside of the human body. Adequate research to completely understand its pathogenesis and the defense of the body against it is still lacking. Diagnosis is often difficult, because the clinical manifestations are widely varied and often imitate many other conditions during each of its many stages of progression.

**FIGURE 7-32**

Syphilis. High-power photomicrograph of tissue from the secondary lesion illustrated in Figure 7-34. Warthin-Starry stain reveals numerous coiled spirochetes.

To add to the diagnostic problems, *T. pallidum* is difficult to visualize microscopically, because it does not absorb the routine screening stains available clinically. Instead, more complex laboratory procedures are required, such as the application of a Warthin-Starry stain (Figure 7-32), a dark-field illumination and detection of the antibodies to the spirochetes tagged with fluorescein dyes and illuminated with UV light.

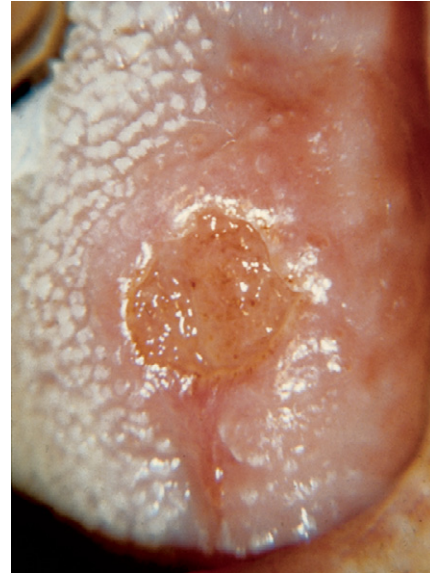
Syphilis

SYPHILIS: A sexually transmitted local and systemic infection caused by *Treponema pallidum* with three progressive clinical stages: (1) a primary chancre at the point of contact, (2) a secondary skin rash and mucous patches, and (3) tertiary (late) systemically disseminated lesions; all are effectively treated with penicillin.

CLINICAL FEATURES

Untreated syphilis progresses through three clinical stages of infection: (1) primary syphilis, (2) secondary syphilis, and (3) tertiary (late) syphilis. The primary and secondary stages are closely associated in time and may even overlap, whereas tertiary or late syphilis may be separated by a period of latency that lasts from several to many years and varies extensively between individuals.

Primary syphilis occurs as a localized lesion at the site of contact and is termed a *chancre*. Chancres occur primarily on the genitals and less commonly within and around the oral cavity (Figure 7-33). In these locations, spirochetes undergo rapid replication and enter the lymphatics and blood stream. An asymptomatic incubation period occurs that averages 21 days, followed by an open wound that teems with spirochetes. At this stage the serologic tests will be negative, but a diagnosis can be made using dark-field or immunofluorescent staining and by

**FIGURE 7-33**

Syphilis. Primary lesion (chancre) of the anterior dorsal tongue at the point of initial contact with a *Treponema pallidum* pathogen. (Courtesy Dr. F.M. Lucartoto.)

**FIGURE 7-34**

Syphilis. Secondary lesion on the ventral surface of the tongue (mucous patch).

microscopically viewing lesional tissue or exudate. Without treatment primary lesions heal in 3 to 6 weeks; with treatment, healing occurs in 10 to 14 days.

Secondary syphilis develops 2 to 6 months after the initial infection if the primary stage is not treated. Some unhealed chancres may still be present. The secondary lesions occur on the skin and mucous membranes and are morphologically diverse. They can occur as macular, papular, follicular, lenticular, papulosquamous, flat papillary (condyloma lata), pustular, nodular, or mucous membrane patches. The lesions may simultaneously appear in many anatomic areas, or they may be localized to one area such as the mucous membranes (Figure 7-34). The lymph nodes are almost always involved at this

stage, and needle aspirates will contain the organisms. The skin and mucous membrane lesions exhibit large numbers of spirochetes; serology tests will be positive. With or without treatment, secondary lesions heal in 2 to 4 weeks. Patients will not be noticeably ill during the secondary stage of the disease.

Tertiary syphilis is also referred to as *late syphilis*. It may occur in some patients despite the apparent, successful treatment of the earlier disease. It involves primarily the CNS and cardiovascular system. This stage has recently been well documented in patients with AIDS; it follows a prolonged period of latency in which the patient periodically experiences some minor exacerbations of the condition. The most serious complication occurs during pregnancy and results in the birth of a fetus with congenital syphilis. In patients with tertiary syphilis, nearly every organ of the body is affected.

Lesions termed *gummas* can destroy the nose, palate, and tongue. In bones the tertiary lesions produce osteomyelitis and destroy joints. The most serious complication of late syphilis is the destruction of the walls of the large blood vessels, resulting in aneurysms and cardiac insufficiency. Neural involvement leads to dementia and strokes.

Congenital syphilis is caused by a transplacental infection with *Treponema pallidum* during fetal development. The extent of involvement varies from an overwhelming infection leading to infant death to an infection with a period of latency in which the disease is not suspected until 12 or more months after birth. In these patients a rash will eventually appear and the destruction of bones, nerves, and some organs will occur. The classic descriptions of saber (pointed) shins, rhagades (perioral vertical creases), frontal bossing, and saddle nose (destruction of the nasal spine) are commonly used to describe the primary manifestations of the infection. **Hutchinson triad** (which consists of blindness, deafness, and dental anomalies) is also used to describe the findings of congenital syphilis. The dental anomalies are the result of failure of some incisal and cuspal growth centers to form. This results in anterior teeth that are narrower at the incisal edge than at the middle third (screwdriver teeth) and notched (Hutchinson teeth), pegged-shaped laterals, and molars with constricted and atrophic cusps (mulberry molars) (Figure 7-35).

DIAGNOSIS

Because primary and secondary manifestations of syphilis have exudative lesions, dark-field examination and direct immunofluorescent staining can be used to facilitate the detection of the organisms. The culture of lesional tissue cannot be used for diagnostic purposes. Screening tests such as the Venereal Disease Research Laboratory (VDRL) test and the rapid plasma reagin (RPR) test are frequently used.



FIGURE 7-35

Congenital syphilis. The patient exhibits anomalously shaped teeth, consisting of incisors with screwdriver-shaped crowns and notched incisal edges and molars with constricted crowns and a lack of cuspal development (mulberry molars).

These tests are not specific for *T. pallidum* and have a risk of false-positive results. More dependable tests are those using antibodies specific for antigenic markers of *T. pallidum*. The most commonly used are the fluorescent treponemal antibody absorption (FTA-ABS) test, the microhemagglutination assay—*T. pallidum* (MHA-TP), and the ELISA.

TREATMENT

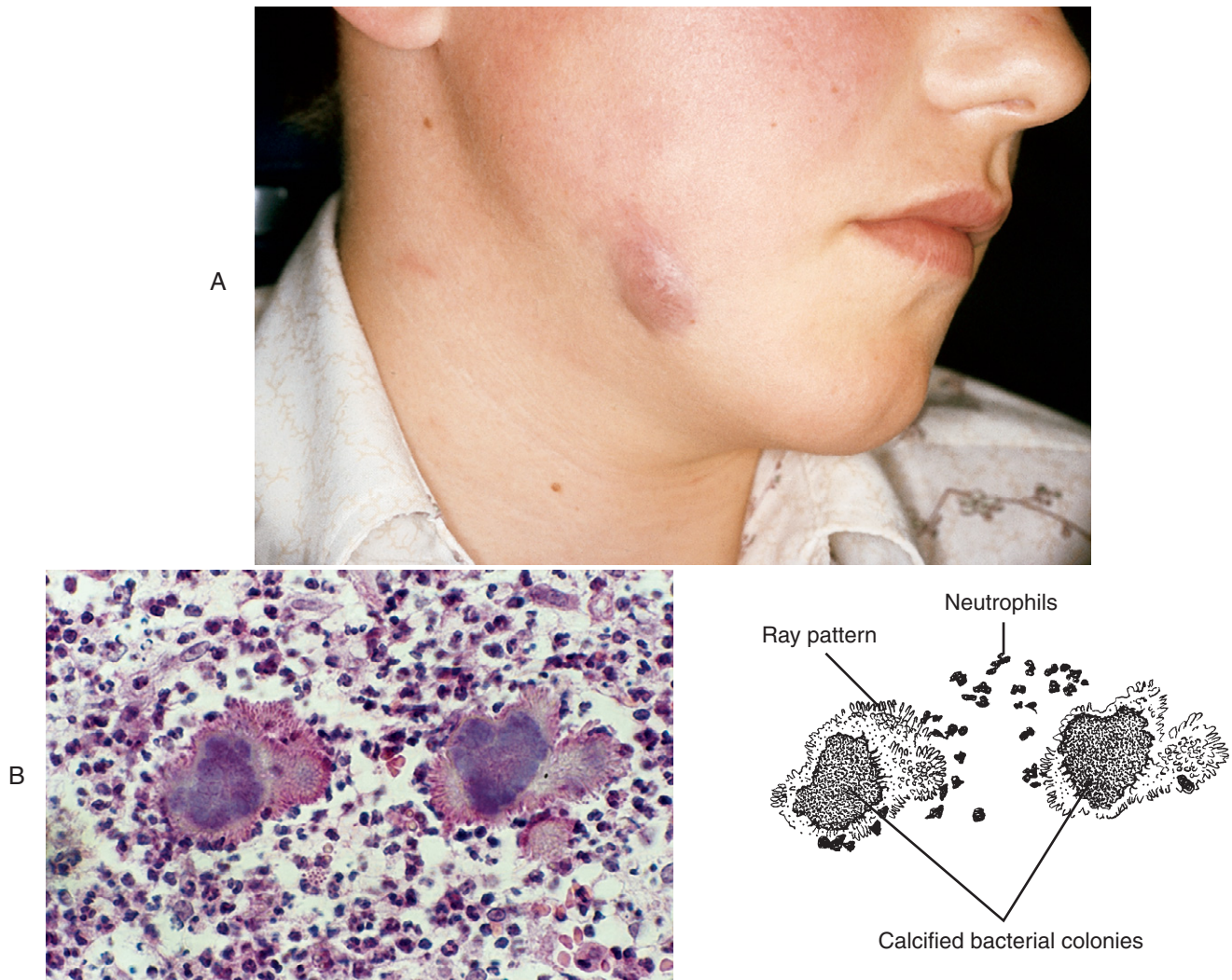
Penicillin G benzathine is the antibiotic of choice and is very effective in the treatment of all stages of syphilis.

ACTINOMYCES

Oral-Cervicofacial Actinomycosis

ORAL-CERVICOFACIAL ACTINOMYCOSIS: An acute deep suppurative abscess of the upper neck, perioral area, and jaws, with an associated draining sinus tract that contains “sulfur granules” and purulent exudate caused by the filamentous anaerobic gram-positive bacteria, *Actinomyces israelii*.

Oral-cervicofacial actinomycosis is caused by an infection by normal commensal (endogenous) organisms of humans and does not require contact with an infected individual. The pathogen is a filamentous bacteria of the genus *Actinomyces*, usually the anaerobic, gram-positive, *Actinomyces israelii*. This family of bacteria includes other members that normally inhabit the oral cavity but are seldom pathogenic. These include *A. naeslundii*, *A. odontolyticus*, and *A. viscosus*. All members of the genus are constituents of dental calculus, the calcified

**FIGURE 7-36**

Oral-cervicofacial actinomycosis. **A**, A young patient with a sinus tract on facial skin caused by an infection of actinomyces after a traumatic injury to the teeth and maxilla 3 months earlier. **B**, Photomicrograph of purulent exudate from a deep abscess composed of neutrophils and containing calcified bacterial colonies with a periphery of filamentous organisms radiating in a sunburst or ray pattern (sulfur granules).

encrustation on teeth. Infections by *A. israelii* are classified according to the anatomic area involved. In most cases, evidence exists of a previous injury or surgical procedure, which allows the organisms to invade an anaerobic environment within the tissue. In the oral, head, and neck areas, the infection is referred to as *oral-cervicofacial actinomycosis*.

CLINICAL FEATURES

The deep infections of cervicofacial actinomycosis are caused by *A. israelii*, normally present in tonsillar crypts, carious teeth, and calculus deposits. Traumatic incidents such as dental extraction, a periapical infection af-

ter an open pulpitis, and a pericoronitis around a partially impacted tooth are potential opportunities for the organisms to become infective. Once infection occurs, an acute inflammatory reaction ensues. In soft tissue, swelling and intense pain are frequent. Bacterial invasion into bone initiates a localized osteomyelitis that can cause a great deal of bone destruction, nodular reactive periosteitis, and soft tissue abscesses that give rise to a regional nodularity with draining sinus tracts on the surface of the skin (Figure 7-36, A) and mucosa. The clinical presentation of the soft tissue has led to the term "lumpy jaw disease." The exudate emanating from the draining sinus tracts will often contain small, clinically

visible yellowish-green calcified structures referred to as sulfur granules. These represent calcified colonies of *A. israelii* and are indicative of actinomycosis.

HISTOPATHOLOGY

The tissue changes in actinomycosis are those of an acute abscess, consisting of a central cavity containing purulent exudate that surrounds multiple calcified colonies of filamentous bacteria. The central area of a colony stains hematoxylin positive and appears somewhat amorphous, whereas the periphery consists of filamentous organisms arranged in a sunburst or ray pattern. The filaments stain positively with both eosin and periodic acid–Schiff (PAS). The surrounding purulent exudate is composed primarily of neutrophils (Figure 7-36, B). The presence of the calcified filamentous bacterial colonies located deep in the tissue is diagnostic for actinomycosis.

TREATMENT

Treatment of actinomycosis consists of surgical drainage and debridement followed by a high daily dose of penicillin for at least 10 days. Large lesions require an extended course of IV-administered penicillin to achieve a complete cure.

MYCOSES

CANDIDA ALBICANS

The genus *Candida* includes eight species of fungi of which *Candida albicans* is by far the most prevalent. *C. albicans* may be present as a yeast (spore); as a yeast with pseudohyphae; or as long, branching septate hyphae. The hyphal form is usually present when organisms are isolated from an infectious process.

Candidiasis is now widely accepted as an encompassing term for the many clinical forms of infection by members of the genus *Candida*. Other synonyms used are *candidosis* and *moniliasis*. All members of the genus are present as commensals that become infective when an alteration in the immunity of the host occurs. Among opportunistic infectious agents, they are usually the first to take advantage of any reduction in the defense system of the host cell.

CLINICAL FEATURES

Within the oral cavity, infections by *C. albicans* occur on the surface of the mucosa where they assume several clinical forms. Some are white and may rub off easily, whereas others do not. Some appear bright red because of atrophy and erosion of the epithelium and an intense inflammation of the underlying connective tissue. A classification of the basic types of oral candidiasis is presented in Box 7-4. Other entities associ-

BOX 7-4

Classification of Basic Types of Oral Candidiasis

ACUTE

Pseudomembranous (thrush)
Atrophic (erythematous)

CHRONIC

Hyperplastic (candidal leukoplakia)

BOX 7-5

Oral Lesions Associated with *Candida Albicans*

Angular cheilitis (perlèche)
Median rhomboid glossitis
Chronic mucocutaneous candidiasis

BOX 7-6

Factors Predisposing Oral Tissues to Candidiasis

Acidic saliva
Xerostomia
Nocturnal denture wearing
Heavy smoking
Blood group O individuals
Immunologic disorders
Antibiotic therapy
Steroid therapy
Iron, folic acid, and vitamin deficiencies
Malnutrition/gastrointestinal malabsorption
Carbohydrate-rich diet
Diabetes mellitus
Human immunodeficiency virus
Endocrine abnormalities
Epithelial dysplasia
Blood dyscrasias and malignancy
Radiation/chemotherapy
Old age/infancy

ated with infections of *Candida albicans* are listed in Box 7-5.

Candidiasis is the classic prototype of an opportunistic infection. It is a commensal organism within the oral cavity that becomes pathogenic when appropriate predisposing factors exist. A large number of factors may predispose the oral tissue to the development of candidiasis (Box 7-6).

Acute Pseudomembranous Candidiasis (Thrush)

ACUTE PSEUDOMEMBRANOUS CANDIDIASIS: A clinical form of *C. albicans* infection that consists of creamy, loose patches of desquamative epithelium containing numerous matted mycelia over an erythematous mucosa that is easily removed; common in patients with more severe predisposing factors.

Acute pseudomembranous candidiasis is characterized by the presence of white curds or creamy, loose patches in various intraoral sites. The white patches can be easily removed with a tongue depressor or gauze (Figure 7-37). The underlying mucosa is erythematous and may bleed slightly. The pseudomembrane consists of desquamative and necrotic epithelial cells and numerous matted and tangled mycelia (hyphae) of *C. albicans*. The lesions are commonly found in newborns before they acquire a competent immune system. Some common causes of this form of candidiasis include the prolonged use of antibiotics, which disrupts the balance in the oral flora; the use of systemic steroids, which induces immunosuppression; HIV infection; chronic xerostomia as the result of radiation therapy, chemotherapy, or medications; Sjögren syndrome; and diabetes mellitus. The diagnosis of candidiasis can be confirmed with PAS-stained cytology smears of the pseudomembrane (Figure 7-38). The matted hyphae will be preferentially stained, allowing the diagnosis to be made rapidly and accurately. To differentiate between the various strains of *Candida* requires the use of immunohistochemical



FIGURE 7-37

Acute pseudomembranous candidiasis (thrush). Tongue exhibits a superficial layer of loose, cream-colored deposit with raised curdlike patches that can be removed, revealing an erythematous base.



FIGURE 7-38

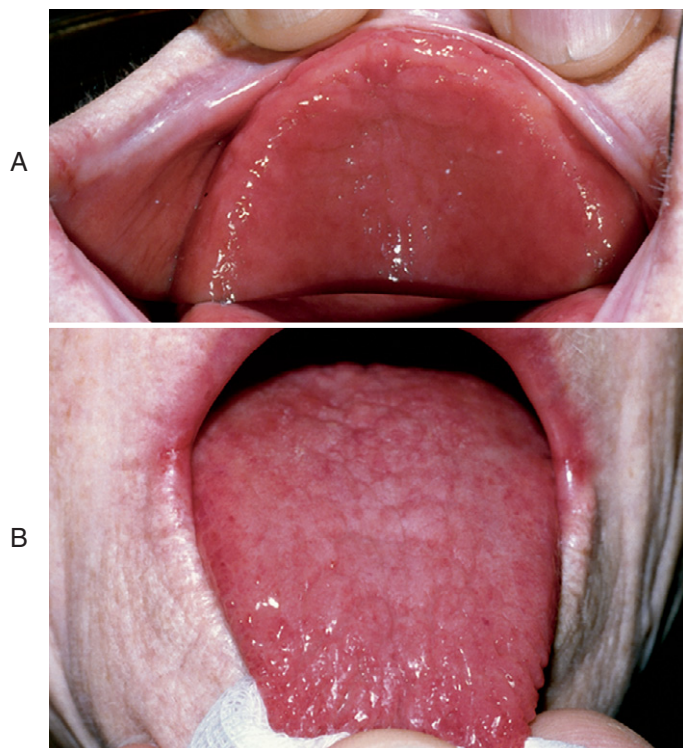
Acute pseudomembranous candidiasis. Cytologic smear of whitish pseudomembrane stained with PAS demonstrating the branching hyphae and budding yeast spores superimposed on desquamated superficial squames.

techniques. Cultures are a much slower method and usually unnecessary in view of the clinical findings and cytologic smear results. Treatment with antifungal medication is effective in relieving symptoms and most infections within 1 to 2 weeks. If lesions do not undergo immediate regression, the patient may be severely immunosuppressed, may be harboring other species of *Candida*, or both. These patients may require more potent medications than the usual azole derivatives such as amphotericin B, which is usually administered IV and requires hospitalization.

Atrophic (Erythematous) Candidiasis

ATROPHIC (ERYTHEMATOUS) CANDIDIASIS: A clinical form of *C. albicans* infection in which the mucosa is thinned, smooth, and bright red with symptoms of burning and increased sensitivity; commonly found on the palate under a denture but also on the tongue and other mucosal surfaces.

In nonimmunosuppressed patients, atrophic (erythematous) candidiasis is most commonly found in patients with ill-fitting dentures or in those who wear their dentures continuously. It has also been referred to as *denture sore mouth* and appears as a generalized red area of atrophic tissue, commonly on the palate (Figure 7-39, A). It is found primarily under maxillary dentures in older patients and more commonly in those patients who do not adequately clean or remove their dentures at night. In the early stages, areas of superficial erosion and petechiae may be present. The chief complaint is of a continuous burning sensation of the affected area. Atrophic candidiasis can also

**FIGURE 7-39**

Atrophic (erythematous) candidiasis. **A,** Intensely erythematous and atrophic mucosa under a maxillary denture that is highly sensitive and periodically painful. **B,** A smooth, beefy-red, sensitive tongue because of the loss of papillae resulting from a long-term persistent candidiasis. Also present is a mild form of *Candida albicans*-induced angular cheilitis (perlèche).

affect the tongue, in which case the tongue exhibits a smooth and beefy-red appearance (Figure 7-39, B). This appearance is due to the loss of the filiform papilla, a generalized thinning of the epithelium, and excessive inflammation of the connective tissue. Patients complain of intense sensitivity and pain on exposure to hot and cold liquids, spicy foods, and alcoholic beverages. Cytology smears usually fail to reveal hyphal forms of the fungal organisms, although careful scrutiny may reveal occasional fungal spore forms. In these cases, cultures may be useful in confirming that a fungal infection is actually present. Because of its distinctive clinical appearance, particularly in a susceptible patient, empirical treatment with antifungal agents in an ointment base applied to the tissue surface of the denture can be instituted. Resolution of the condition over a period of 1 to 2 weeks confirms the diagnosis. To achieve a long-term cure, the predisposing factors need to be identified and corrected and the existing infection needs to be topically or systemically treated.

Chronic Hyperplastic Candidiasis

CHRONIC HYPERPLASTIC CANDIDIASIS: A clinical form of *C. albicans* infection consisting of white plaques or papules against an erythematous background containing hyphae in the parakeratin layer of the thickened epithelium.

Chronic hyperplastic candidiasis usually presents as a white mucosal plaque. It is most commonly found on the buccal mucosa along the occlusal line in a V-shape widening as it approaches the commissure (Figure 7-40). Other common locations are the laterodorsal surfaces of tongue and the alveolar ridges. Because it appears as a mucosal white patch or plaque, it is frequently termed “candidal leukoplakia.” The lesion is often discovered during the microscopic evaluation of a routine biopsy of a leukoplakic lesion, when the hyphal forms of the organism are observed. At times, chronic hyperplastic candidiasis presents as white papules against an erythematous background and resembles a speckled leukoplakia or speckled erythroplasia conditions that commonly exhibit microscopic features of epithelial dysplasia. Because of its close clinical resemblance to a premalignant lesion, biopsy is necessary.

Tissue specimens usually exhibit hyperparakeratosis containing variable numbers of hyphae that vertically invade the parakeratin. Although the hyphae can often be seen with routine H&E stains, most cases require

**FIGURE 7-40**

Chronic hyperplastic candidiasis (candidal leukoplakia). Localized white mucosal patch that is asymptomatic and does not rub off on the mucosa adjacent to the commissure.

PAS or silver stains to demonstrate their presence. Variable numbers of neutrophils, sometimes occurring as microabscesses (Munro abscesses) within the parakeratin layer, are commonly seen. The spinous layer of the epithelium usually thickens (acanthosis), and the rete pegs become longer. The underlying connective tissue exhibits an inflammatory infiltrate consisting of plasma cells and lymphocytes.

Because the fungal organisms are found on or near the epithelial surface, topical antifungal medication is more effective than medication administered for systemic effect. Because candidiasis is an opportunistic infection, attempts should be made to identify and correct predisposing factors to prevent recurrence.

Angular Cheilitis (Perlèche)

ANGULAR CHEILITIS (PERLÈCHE): Symptomatic bilateral fissures of the corners of the mouth that are common in patients with *C. albicans* infection in other parts of the mouth and often intensified with mouth overclosure; requires treatment with antifungal medication.

Angular cheilitis is a bilateral chronic inflammation of the corners (angles) of the mouth, characterized by atrophy and linear fissures (Figure 7-41). Although the lesions may occur alone, they are often associated with intraoral acute pseudomembranous or atrophic lesions in other parts of the mouth. Angular cheilitis is common in patients with a loss of vertical dimension because of tooth loss, attrition of teeth, or old dentures.

Secondary infections with bacteria sometimes occur, complicating treatment. In the past this lesion was con-



FIGURE 7-41
Angular cheilitis (perlèche). Severe fissures in the corners (angles) of the mouth in a patient with adult onset diabetes mellitus.

sidered a sign of vitamin-B deficiency; treatment efforts were often erroneously directed toward correcting only that condition. Although jaw overclosure may mechanically intensify angular cheilitis and provide a favorable environment for growth, it is not the sole cause. Treatment consisting only of increasing the vertical dimension is insufficient to correct the problem. As with all lesions of candidiasis, treatment is a twofold process that consists of identifying the predisposing factors and eradicating local infection. Antifungal ointments alone or in combination with antibiotics, if a bacterial infection is present, are usually effective in treating angular cheilitis.

Median Rhomboid Glossitis

MEDIAN RHOMBOID GLOSSITIS: An asymptomatic, elongated, erythematous patch of atrophic mucosa of the middorsal surface of the tongue because of a chronic *C. albicans* infection.

Median rhomboid glossitis represents an area of chronic candidiasis located on the middorsum of the tongue. In the past it was thought to represent a developmental defect and was therefore not treated. The lesion starts as a narrow, mildly erythematous area located along the median fissure of the tongue (Figure 7-42). The lesion is asymptomatic and enlarges slowly, often remaining unnoticed by the patient for many years. If undiagnosed and untreated, the lesion gradually enlarges and exhibits the erythematous nodular hyperplasia characteristic of chronic hyperplastic candidiasis. In some patients a lesion develops on the midline of the palate opposite the tongue lesion.

Because median rhomboid glossitis can be clinically suspicious, it is occasionally biopsied. Treatment



FIGURE 7-42
Median rhomboid glossitis. The localized midline area of atrophy and erythema is usually asymptomatic, present for prolonged periods, and gradually increases in size with the surface becoming increasingly pebbly or nodular. Hyphae of *Candida albicans* are commonly found in the parakeratin layer.

consists of identifying and managing predisposing factors and the application of topical antifungal agents for prolonged periods.

For convenience, the clinical term *chronic multifocal oral candidiasis* is sometimes used to describe patients exhibiting more than one of the previously mentioned chronic forms of candidiasis. Lesions may persist for many years but do not usually involve other anatomic sites. The reason for the site specificity of these low-grade infections is not known. The intervening mucosa is unaffected. Many of the patients are smokers, denture wearers, or both. Unless the predisposing factors are identified and corrected, treatment with an antifungal medication is effective only as a temporary measure.

Chronic Mucocutaneous Candidiasis

Chronic mucocutaneous candidiasis (CMC) is a term used to describe a condition in which persistent and refractory candidiasis occurs on the mucous membranes, skin, and nails of the affected patients (Figure 7-43). Most of these patients exhibit endocrinopathies or defects of the immune system.

HISTOPLASMA CAPSULATUM

Histoplasmosis

HISTOPLASMOSIS: A chronic lung infection common in the Mississippi Valley caused by inhalation of spores of *Histoplasma capsulatum*; may have associated intraoral lesions consisting of a chronic ulcer clinically resembling a malignancy and is best treated with amphotericin B.

Histoplasmosis is a deep mycotic infection in which the organism *H. capsulatum* infects the lungs through inhalation of airborne spores (conidia). Fortunately most cases are asymptomatic, and only 1% of the infected hosts develop a clinically detectable pneumonia. In even fewer cases the disease disseminates to other organs and tissues. Histoplasmosis occurs throughout the temperate zones of the world. In North America, endemic areas are located in the Mississippi and Ohio River Valleys of the United States. Endemic areas are also found in various locations in Central and South America. The organisms are present as saprophytic spores found in soil contaminated by bat and bird droppings. Inhalation of spores occurs when the dust and soil of attics, caves, and other roosting areas of birds and bats are disturbed. In some endemic



FIGURE 7-43

Chronic mucocutaneous candidiasis. A patient with refractory candidiasis of the oral mucous membranes (A), eyelids (B), and skin surrounding the nail bed (C).

areas 70% of the inhabitants will have positive skin tests, yet few will recall having acquired the infection.

CLINICAL FEATURES

Patients with symptoms of infection exhibit a short, transient period of fever, malaise, cough, and dyspnea. Immunity develops rapidly in nearly all patients. In the rare instances in which the immunity of the patient does not arrest or otherwise contain the disease, granulomas and cavitation of lung tissue occurs, often followed by dissemination of the disease to the regional lymph nodes and adjacent anatomic structures. In chronic forms of the disease, dissemination to the skin and oral mucous membranes may be the first signs of infection.

Oral lesions of histoplasmosis occur primarily on the gingiva, tongue, palate, and buccal mucosa. The lesions are granulomatous and appear initially as a nodule and later as a chronic ulcer with raised, rolled borders and induration of the surrounding tissue (Figure 7-44). The clinical appearance closely resembles that of carcinoma or tuberculosis. On the gingiva it may appear as a diffuse granulomatous process with underlying alveolar bone loss and loosening of teeth. Because lesions can resemble many other conditions, histoplasmosis is seldom suspected initially. The diagnosis is usually determined after laboratory examination of an incisional biopsy. In patients with immunodeficiencies, lesions of histoplasmosis may be multiple and widely disseminated. Cervical lymphadenopathy is common, and brain involvement may occur.

HISTOPATHOLOGY

Histoplasmosis is a granulomatous infection characterized by the formation of multiple, small, often inconspicuous granulomas composed of histiocytes, many of which contain variable numbers of organisms. A gener-



FIGURE 7-44

Histoplasmosis. A lesion of the palate in a patient with AIDS that exhibits an irregularly shaped deep ulcer with central necrosis over granulation tissue.

alized background of histiocytes, lymphocytes, and plasma cells often obscures the granulomas. Scattered multinucleated giant cells may be present (Figure 7-45, A). The organism is usually present in its spore form, measures 2 to 5 μ m in diameter, and is located within the histiocytes and multinucleated cells and interspersed among the other inflammatory cells. With routine H&E tissue stains, spores can only be seen when present in large numbers. However, they are more easily visualized with PAS (Figure 7-45, B) and methenamine silver stains, which selectively stain the small spores.

DIAGNOSIS

Histoplasmosis is diagnosed by combining data obtained from clinical evaluation, microscopic examination, culture, serologic findings, and the histoplasmin skin test. The histoplasmin skin test uses inactivated mycelia or yeast of the organism but is not an effective test in endemic areas of the world where a large proportion of the population has had subclinical contact with the spores

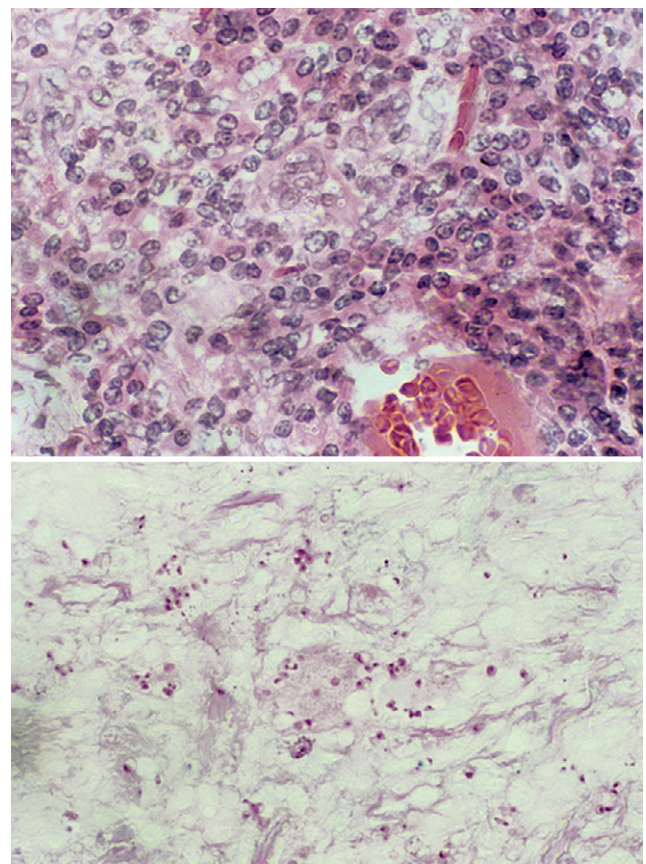


FIGURE 7-45

Histoplasmosis. A, Photomicrograph of hematoxylin and eosin (H&E)-stained granulomatous tissue composed of histiocytes and occasional multinucleated giant cells. B, Same tissue with periodic acid-Schiff stain reveals numerous small spores of *Histoplasma capsulatum* (small red dots).

and has antibodies to the organisms. The most sensitive and reliable test for histoplasmosis is the immunodiffusion test, which detects the patient serum antibody to the H and M antigen of *H. capsulatum*. DNA probes are also available.

TREATMENT

Immunocompetent patients without CNS involvement can be initially treated with itraconazole or ketoconazole and are usually treated for 6 to 12 months. For more disseminated histoplasmosis, administration of amphotericin B remains the therapy of choice. In patients with immunodeficient disorders such as AIDS, recurrence of the infection is a continuing problem.

COCCIDIoidES IMMITIS

Coccidioidomycosis

COCCIDIOIDOMYCOSIS: A chronic lung infection caused by inhalation of spores of *Coccidioides immitis* common in the San Joaquin Valley of California; may have associated chronic ulcers in the mouth resembling a malignancy; best treated with amphotericin B.

Coccidioidomycosis is a deep fungal infection of lungs that is common in patients in the arid parts of North and South America and is caused by inhaled spores of *C. immitis* present in dust. One of the largest endemic areas for this disease is in the central valley of California, where it is known as *San Joaquin Valley fever* or simply *valley fever*. Other endemic areas in North America include the Maricopa and Pima counties of Arizona, parts of southwest Texas, and northern Mexico.

CLINICAL FEATURES

Approximately 40% of individuals exposed to *C. immitis* will develop significant lung and respiratory symptoms, fever, cough, chest discomfort, and arthralgia at the time of initial exposure. A small percentage of these patients will develop disseminated disease. Fatal outcomes are rare unless the patient is severely immunocompromised.

Disseminated organisms may involve the skin and oral mucous membranes. Intraorally, the mucosal lesions usually resemble other granulomatous diseases, with ulceration and induration as prominent features. As with other deep fungal infections, clinical distinction from carcinoma is not possible, and microscopic examination of a tissue sample and testing for seroimmunoreactivity is therefore essential.

HISTOPATHOLOGY

Coccidioidomycosis is characterized by multiple focal granulomas containing large macrophages, lymphocytes, plasma cells, and multinucleated giant cells. Liq-

uefactive necrosis and exudate may be seen in the center of the granulomas. PAS and methenamine silver stains reveal large spherules (10 to 60 μ m in diameter) filled with endospores measuring 2 to 5 μ m in diameter.

DIAGNOSIS

The diagnosis of a *C. immitis* infection uses fractions of the organism in the mycelial phase (coccidioidin) and the spherule phase (spherulin) as antigens to test for the presence of the antibody. A positive skin reaction can be observed 2 to 4 weeks after the patient has had contact with the organism. Serum antibody levels can be monitored by immunodiffusion and latex particle agglutination tests.

TREATMENT

Itraconazole or fluconazole can be effective in more indolent infections. Recurrence is often a problem after cessation of azole therapy. Permanent cures usually require amphotericin B therapy, particularly in the more serious infections.

CRYPTOCOCCUS NEOFORMANS

Cryptococcosis

CRYPTOCOCCOSIS: A chronic infection of the lungs caused by the inhalation of spores of *Cryptococcus neoformans* carried in bird droppings, with a predilection for spread to the CNS; oral chronic ulcers primarily occur in immunocompromised patients and are best treated with amphotericin B.

C. neoformans, the causative organism of cryptococcosis, is a universally distributed fungus that is present in the droppings of pigeons. As in most deep fungal infections, the spores are transmitted as aerosols through the respiratory passages into the lungs, where primary lesions occur. Of particular concern with infections of *C. neoformans* is the predilection for spreading to the CNS.

CLINICAL FEATURES

Most patients are not aware of initial contact with *C. neoformans*, whereas others may experience mild flu-like symptoms. In some patients the primary lung infection results in a residual nodule that can be mistaken for a carcinoma. CNS involvement is usually in the form of a severe meningitis, but on occasion granulomas that produce neurologic defects are located within the brain. Oral lesions usually occur in patients who are severely immunosuppressed or suffering from leukemia or lymphoma. The lesions present as ulcers and granulomas that penetrate into bone or perforate the palate.

HISTOPATHOLOGY

Tissue contains multiple focal granulomas exhibiting numerous lymphocytes and plasma cells. Macrophages and multinucleated giant cells containing fungal organisms are present in clusters or singly throughout the lesion. The infective form of the fungus is a budding yeast that measures 5 to 20 μ m in diameter and exhibits a thick mucicarmine-positive capsule that resembles a halo.

TREATMENT

The treatment of choice for cryptococcosis is amphotericin B, which is usually supplemented with 5-fluorocytosine when neurologic involvement is present. After this initial treatment, patients are placed on longer-term fluconazole. In many cases, particularly in the immunosuppressed patient, relapse is a problem after therapy stops.

BLASTOMYCES DERMATITIDIS

North American Blastomycosis

NORTH AMERICAN BLASTOMYCOSIS: An uncommon, rarely symptomatic, chronic lung infection caused by inhalation of spores of *Blastomyces dermatitidis*; has associated skin lesions and occasional chronic mouth ulcers that resemble malignancy and are best treated with amphotericin B.

Blastomycosis is caused by *B. dermatitidis* and occurs predominantly in patients in North America and parts of Africa. As with other deep mycotic infections, a primary infection of the lungs results from the inhalation of spores. The exact reservoir of the organisms is still un-

known. Attempts to culture organisms from the soil in endemic areas have been unsuccessful.

CLINICAL FEATURES

Similar to many other deep mycoses, most of the primary infections of blastomyces are asymptomatic. When symptoms do occur, they are usually flulike in nature unless a disseminated infection occurs. Skin involvement is common, beginning as a rash or papular eruptions that become pustular and eventually ulcerative. Intraoral lesions are crateriform and indurated, simulating a squamous cell carcinoma.

HISTOPATHOLOGY

Cutaneous or mucosal lesions are characterized by a central ulcer, and the adjacent epithelium exhibits a pseudoepitheliomatous hyperplasia, which may lead to an erroneous suspicion of malignancy. The connective tissue is granulomatous, consisting of histiocytes, lymphocytes, plasma cells, and multinucleated giant cells. Budding spores measuring 8 to 15 μ m in diameter are found in areas of inflammation, particularly within the cytoplasm of multinucleated giant cells (Figure 7-46).

DIAGNOSIS

Although not entirely specific, two antigenic tests based on the use of fractions of *B. dermatitidis* in the mycelial (blastomycin) and yeast phases are available. Immunodiffusion tests are more reliable but are technically difficult to perform. The microscopic and culture appearances of the organism are important in making the diagnosis.

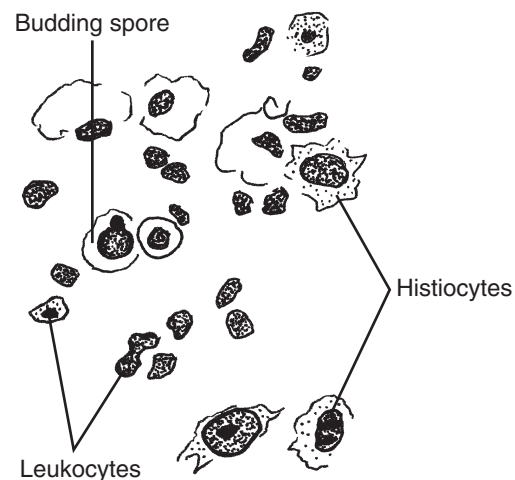
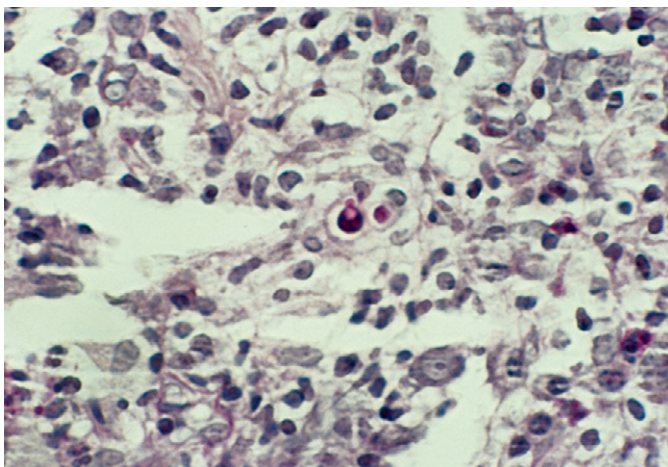


FIGURE 7-46

Blastomycosis. A photomicrograph of granulation tissue from the base of a chronic ulcer with periodic acid-Schiff stain, revealing the presence of a budding spore (center area) typical of *Blastomyces dermatitidis* with surrounding histiocytes, multinucleated giant cells, and leukocytes.

TREATMENT

Patients with uncomplicated lung infections and without meningeal lesions can be treated with oral itraconazole. Otherwise the treatment of choice for blastomycosis is IV-administered amphotericin B.

ASPERGILLUS**Aspergillosis**

ASPERGILLOSIS: An infection commonly located in the lungs of immunocompromised patients and occasionally occurring as a destructive lesion of the maxillary sinuses, anterior palate, and nasal passages as the result of the inhalation of spores of *A. fumigatus* and *A. flavus*; best treated in the oral area with surgical debridement followed by amphotericin B and azole fungicides and with management of the predisposing condition.

Aspergillosis is caused by the *Aspergillus* species of fungi. The species most frequently found in opportunistic infections are *A. fumigatus* and *A. flavus*. Usually, healthy individuals are not susceptible to infection with this organism. Although the fungal spores are widespread in the environment, they are not part of the human flora. *Aspergillus* is a major cause of mycotic infections in domestic farm animals and birds, in which it remains as a large reservoir. Acquisition of an infection with this organism by humans requires a severely compromised or debilitated host, such as occurs in those with AIDS and in immunosuppressed organ transplant recipients.

CLINICAL FEATURES

Human infections by *A. fumigatus* are increasing as a result of the growing number of patients who take immunosuppressive drugs for organ transplantation and

the growing population of immunodeficient patients. In these patients, infection usually occurs in the lungs and is manifested by the formation of a “fungus ball.” In the oral area nearly all cases involve the anterior palate, nasal spine and passages, and maxillary sinuses. In these areas, swelling is a common presenting symptom that has a radiographic appearance characterized by dense radiopacities within an area of bone destruction. Lesions may extend to the floor of the orbit, resulting in visual disturbances.

HISTOPATHOLOGY

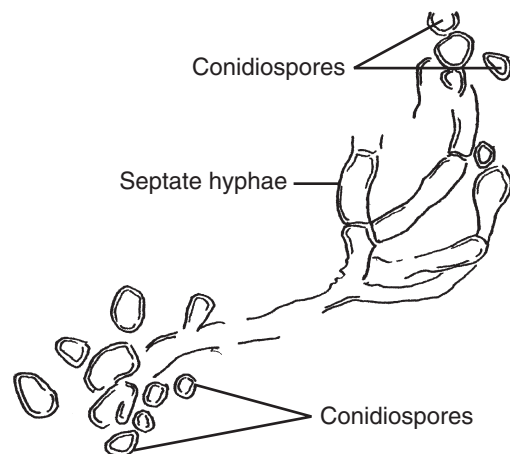
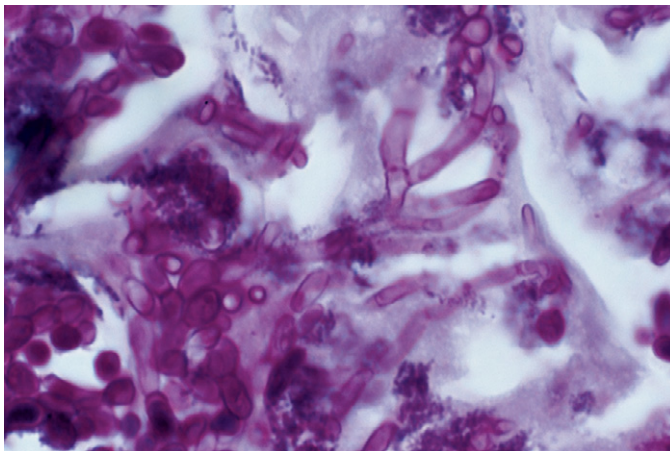
The organisms are usually present in the center of an area of necrosis and exudate, which is surrounded by a typical granulomatous reaction with dense infiltrates of histiocytes, lymphocytes, and plasma cells. The presence of the fungus is demonstrated with PAS or methenamine silver stains, which reveal large branching septate hyphae, conidiophores, and conidiospores (Figure 7-47).

DIAGNOSIS

The diagnosis of aspergillosis in humans relies heavily on the clinical circumstances of the infection, the anatomic site of the infection, and the microscopic findings. Culture is difficult and is often negative. No skin sensitivity or serum reactivity tests are useful, because most of the affected patients are immunodeficient.

TREATMENT

A major component of the treatment of aspergillosis is the surgical debridement of the sequestered bone and necrotic tissue in which the organisms reside. To be effective, aggressive treatment with amphotericin B and azole systemic fungicides is necessary. Until the underlying predisposing factors are corrected, the prognosis is not favorable.

**FIGURE 7-47**

Aspergillosis. Photomicrograph of tissue from a fungus ball of maxillary sinus stained with periodic acid–Schiff, revealing the septate hyphae with conidiospores.

ZYGOMYCOTA MUCOR AND RHIZOPUS

Rhinocerebral Zygomycosis

RHINOCEREBRAL ZYGOMYCOSIS: A chronic destructive infection of the midface and nasal passages, occurring in patients with uncontrolled diabetes mellitus, neutropenia, and severely compromised immune systems; caused by members of *Mucor* or *Rhizopus* of the phylum Zygomycota; best treated with surgical debridement, followed by amphotericin B and management of the predisposing condition.

Zygomycosis is caused by fungal organisms of the phylum Zygomycota that contains the genera *Mucor* and *Rhizopus*; this is the same order of fungi that constitutes the mold on bread and fruit. Collectively, human infections by these organisms are termed *zygomycosis*, because any one of a large number of the members of this phylum may be involved. In the past they were termed “**phycomycosis**,” reflecting an older term for one of the genera. More recently they were referred to as “**mucormycosis**,” the name of one of the orders of Mucorales.

The spores from these molds are transmitted by inhalation, via a variety of percutaneous routes, or by ingestion. Although the organisms may produce lung and skin infections, the most common human disease process produced is *rhinocerebral zygomycosis*, so named because it primarily affects the nose, maxillary sinus, and midface, with frequent extension to the brain.

CLINICAL FEATURES

The fungi responsible for zygomycosis flourish in an acidic environment, usually in patients with severe ketoacidosis because of uncontrolled diabetes mellitus. Other host risk factors include neutropenia, sustained immunosuppressive therapy, chronic steroid use, iron chelation treatment, broad-spectrum antibiotic use, and severe malnutrition. The fungus tends to invade and block major blood vessels, resulting in ischemic necrosis, gangrene, and large tissue defects.

HISTOPATHOLOGY

The typical microscopic features of zygomycosis include extensive tissue necrosis and the presence of numerous large fungal hyphae. The hyphae are coenocytic (non-septate) and can be seen with routine H&E stains. They exhibit a ribbonlike appearance, with budding and dichotomous branching (Figure 7-48). Numerous sporangiospores are also present.

TREATMENT

Treatment of zygomycosis is similar to that of aspergillosis, consisting of surgical curettage, aggressive therapy with amphotericin B, and management of the underlying predisposing condition.

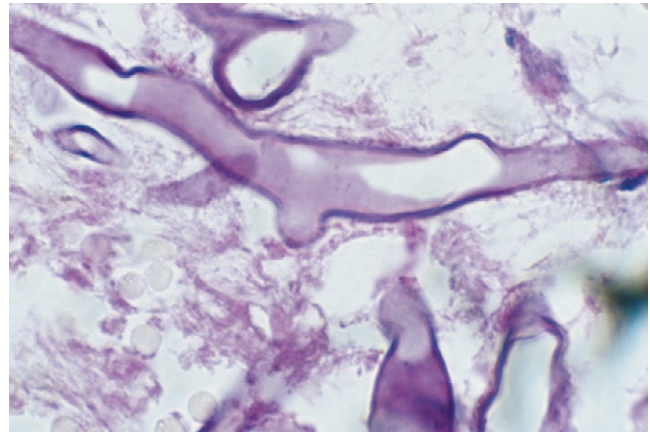


FIGURE 7-48

Zygomycosis. Photomicrograph of hematoxylin and eosin (H&E)-stained tissue from an immunosuppressed patient with a destructive lesion of the anterior maxilla, revealing large ribbonlike tubular nonseptate structures budding at right angles against a background of necrotic debris.

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CHAPTER OUTLINE

RECURRENT APHTHOUS STOMATITIS

Associated Systemic Conditions
Aphthous Minor
Aphthous Major
Herpetiform Ulcers
Behçet Syndrome

MUCOSAL AND SKIN CONDITIONS

Lichen Planus
Lichenoid Reactions
Mucous Membrane Pemphigoid
Pemphigus Vulgaris
Epidermolysis Bullosa
Erythema Multiforme
Lupus Erythematosus
 Systemic Lupus Erythematosus
 Subacute Cutaneous Lupus
 Erythematosus
 Discoid Lupus Erythematosus
Progressive Systemic Sclerosis

ALLERGIC REACTIONS

Contact Stomatitis
Angioedema

POSSIBLE IMMUNE-MEDIATED REACTIONS

Cheilitis Glandularis
Orofacial Granulomatosis
 Oral Crohn Disease
 Cheilitis Granulomatosa
 Melkersson-Rosenthal Syndrome
Chronic Granulomatous Disease
Sarcoidosis
Pyostomatitis Vegetans
Wegener Granulomatosis

ADDITIONAL KEY TERMS

Anaphylactic shock
Desquamative gingivitis
Graft-versus-host disease
Keratin mucopolysaccharide dystrophy
Koebner phenomenon
Lichenoid dysplasia
Nikolsky sign
Suprabasilar bullous formation
Tzanck cells



Although most of the diseases discussed in this chapter are considered to be of immune system origin, future clinicians may identify specific exogenous causative agents for some or all of them. Regardless of the initiating agents, the same immune system designed to protect the body may, on occasion, contribute substantially to the development and magnitude of disease processes. Common to most of the inflammatory reactions in the diseases discussed is the dominance of the cellular component of the immune response, chiefly lymphocytes. When disease mainly targets the surface epithelium, it is characterized by a substantial increase in the number of Langerhans cells—an integral part of the cellular component of the intraepithelial immune system. Langerhans cells are antigen-processing cells, with a role equivalent to that of the macrophages of connective tissue. Their role is to initiate a cascade of cellular and humoral immune responses. In many of the diseases discussed in this chapter, antibodies against normal mucosal and skin epithelium can also be found circulating in the blood, providing further evidence that these diseases are autoimmune in origin. These findings have prompted continuing research for exogenous agents capable of penetrating the skin and mucosal barrier, stimulating Langerhans cells and altering normal antigenic determinants to the extent that antibodies are produced against the body's own tissue.

RECURRENT APHTHOUS STOMATITIS

Recurrent aphthous stomatitis (RAS) is a common disease in humans. Within the oral cavity, RAS is the most common condition affecting the mucosal soft tissue. Approximately 15% to 20% of the world population is afflicted by this condition. It appears to be more common in North America, where specific socioeconomic and age groups reveal incidences of nearly 40%. The peak age of onset for RAS is between 10 and 19 years. In some patients, after childhood and adolescence, lesions may continue throughout the entire lifespan. In the English-speaking world the lesions are commonly known as "canker sores" and are often confused with recurrent herpes simplex infections. RAS is an enigma to researchers, because clinical lesions that occur in association with a large number of disparate local and systemic conditions are found to have a single pattern of histopathologic features. This has led many researchers to view the lesions of RAS as a common mucosal manifestation of many different disease processes, each of which is mediated through the immune system. In some conditions, similar lesions can be found on the mucosal surfaces of the anogenitalia. Within the oral cavity, RAS occurs in three distinct clinical forms: (1) aphthous minor, (2) aphthous major, and (3) herpetiform ulcers. RAS also occurs

in association with chronic gastrointestinal (GI) disturbances and other systemic conditions, the most notable of which is Behçet syndrome.

Aphthous ulcers are usually diagnosed based on their clinical signs and symptoms, because no reliable laboratory tests exist. During a brief preulcerative phase, a subtle and specific microscopic change is sometimes present that may aid in diagnosis. Once ulceration occurs, tissue changes are nonspecific and resemble those seen in an ulcer caused by many other conditions.

ASSOCIATED SYSTEMIC CONDITIONS

The majority of patients with recurrent aphthous ulcers are otherwise healthy. In a minority the presence of chronic RAS lesions is associated with a systemic condition. The systemic conditions most consistently associated with chronic and recurring aphthous lesions are Behçet syndrome and the chronic GI malabsorption disturbances, particularly Crohn disease and gluten-sensitive enteropathy (celiac disease). Often the malabsorption syndromes are mild or even symptomless but still appear capable of producing nutritional deficiencies of folic acid, vitamin B12, and iron, all of which have been implicated in patients with chronic recurrent aphthous ulcers.

Many patients can correlate ulcerative episodes with the ingestion of certain foods, most notably nuts and chocolate, whereas others have chronic asthma, multiple allergies, or both. Correlation has been found with the menstrual cycle, periods of stress and anxiety, and a family history of lesions. It has recently been discovered that patients who are immunodeficient, particularly those that are positive for the human immunodeficiency virus (HIV), become prone to prolonged, severe attacks of aphthouslike lesions. Because of the wide variety of associated conditions, no unifying theory of pathogenesis (other than that the lesions appear to be related to the immune system) has yet evolved.

APHTHOUS MINOR

APHTHOUS MINOR: Commonly encountered, painful, small, superficial ulcers of the oral gland-bearing mucosa that occur episodically in clusters of one to five lesions.

Aphthous minor is the clinical form of virtually all RAS lesions. The other forms, major and herpetiform, together are estimated to occur less than 5% of the time.

CLINICAL FEATURES

Oral lesions of RAS minor occur episodically, with less than five ulcers present at any one time. During an attack, new lesions may continually appear for a 3- to 4-week period, with each lesion lasting 10 to 14 days. The ulcers are located on the gland-bearing mucosa, usually sparing the

attached gingiva, hard palate, and dorsum of the tongue. Individual lesions are round but may be elliptical if they are located in a crease or fold of the tissue. Individual lesions are small (0.5 mm to 1.0 cm in diameter) and shallow, with sharp crateriform edges, whitish-yellow bases, and erythematous halos or flares on the surrounding mucosa (Figure 8-1). Patients complain of pain that is out of proportion to the size of the lesion. The most common locations for lesions are the mucosal surfaces of the lips, posterior soft palate, and anterior fauces. Other less common locations are the ventral and lateral borders of the tongue and the anterior floor of the mouth.

When lesions occur on the labial mucosa, a history of a minor traumatic incidents can often be elicited. In some lesions, multiple malaligned teeth with sharp incisal edges, particularly cuspids that are labially displaced, are present in the area in which patients usually experience lesions. Although mechanical irritants are not known to be the cause of aphthous ulcers, they often seem to precipitate the appearance of individual aphthous ulcers during an episodic period. Lesions of the soft palate and ventral tongue usually appear spontaneously without known precipitating traumatic incidents.

The clinical course of minor aphthous ulcers differs significantly from minor lacerations of the mucosa of nonaphthous-prone individuals. Traumatic breaks in the mucosa of nonaphthous patients will exhibit some tenderness for 1 or 2 days and heal uneventfully in 5 or 6 days. When slight and superficial mucosal lacerations occur in patients with a predisposition for aphthous ulcers, tenderness intensifies to pain in a few days and continues to intensify for 7 to 10 more days before finally healing in 10 to 14 days. Between episodes, patients subject to RAS have normal reactions and healing times for minor lacerations. Surgi-

cal procedures on the mucosa during an aphthous attack heal normally.

HISTOPATHOLOGY

Mild tissue changes can be found during the preulcerative or prodromal stage. They consist of a mild infiltrate of T4 helper and induce lymphocytes concentrated in perivascular locations of the submucosal tissue. Later, T cells are observed within the epithelium, with vacuolization and necrosis of individual epithelial cells that eventuates in epithelium disintegration and ulceration. During this second phase the underlying connective tissue contains dense infiltrates of T8 suppressor and cytotoxin. The perivascular infiltrates are found more deeply in the submucosal tissue than normally occurs during the inflammatory cellular response to minor lacerations in nonaphthous patients. The ulcer surface is covered by a fibrinopurulent exudate overlying a zone of granulation tissue in which neutrophils, macrophages, and plasma cells are prominent, but mast cells and eosinophils are found in scant amounts (Figure 8-2). Normal healing occurs when epithelium migrates over fibrous tissue. During this final phase the predominant lymphocyte subset reverts back to a T4 population.

TREATMENT

The treatment of recurrent aphthous ulcers is varied, with proponents for each of a wide variety of remedies. Because no treatment exists to prevent a predisposition for future attacks, treatments are directed toward reducing the intensity and length of each episode. The most successful treatment is the application of gel- or cream-based topical steroids, particularly those on the higher end of the potency scale. In severe and persistent cases the administration of systemic steroids for 1 week has been shown effective. When only a few lesions are present in the parts of the mouth accessible to the patient,



FIGURE 8-1
Recurrent aphthous minor. Lesions are shallow crateriform ulcers with a whitish-yellow base and an erythematous halo.

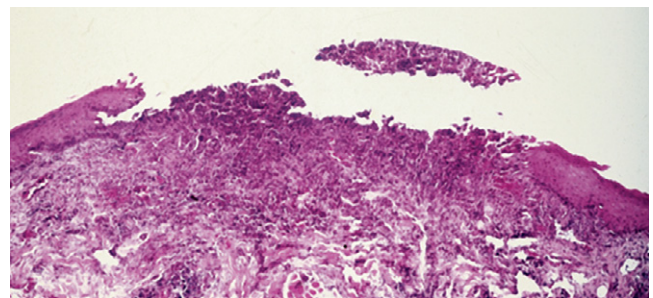


FIGURE 8-2
Recurrent aphthous minor. Microscopic appearance of the ulceration exhibiting a fibrinopurulent exudate over granulation tissue containing an infiltrate of mixed acute and chronic inflammatory cells.

self-administered chemical cautery or styptic agents (e.g., powdered alum, powdered boric acid) have been used to reduce the duration of lesions. In addition to sterilizing the wound, these agents produce a layer of the patient's own devitalized tissue that acts as an occlusive "bandage" over the lesion, separating the oral environment from the immune response of the tissue. Although this does not prevent new lesions from occurring, it helps the patient by reducing the duration of the lesions. Oral rinses containing antimicrobials (chlorhexidine, tetracycline) provide short-term relief in some patients; when used on a daily basis during recurring bouts, they serve to lengthen the period between episodes. If patients are found deficient in folic acid, vitamin B12, or iron, dietary supplementation is sometimes useful. Patients found to be gluten-sensitive require long-term dietary modification. Reduction of oral lesions often coincides with the improvements to the GI tract.

APHTHOUS MAJOR

APHTHOUS MAJOR: One or two uncommon, large, superficial, painful ulcers; usually appear on the labial mucosa and soft palate.

Aphthous major is uncommon but is still the second-most-common form of RAS. It was previously referred to as "periadenitis mucosa necrotica recurrens," reflecting the propensity of the lesions to occur over areas of mucosa containing a large number of minor salivary glands.

CLINICAL FEATURES

Lesions are large, compared with aphthous minor, ranging from 5 to 20 mm or more in size. They occur in fewer numbers, usually only one or two at a time and primarily in two locations—the mucosa of the lips (Figure 8-3, A) and the posterior soft palate and anterior fauces area (Figure 8-3, B). Lesions are crateriform, deeper than aphthous minor lesions, and last for much longer periods (often up to 6 weeks). Pain is severe, making eating difficult, particularly when lesions are located in the posterior aspect of mouth. Aphthous major ulcers usually do not occur until after puberty; in some patients they may be a problem for as long as 20 years. Deep and persistent lesions may become secondarily infected with bacterial and fungal organisms. When healing occurs, scar formation with tissue contracture often results. This is an unusual occurrence on oral mucosal surfaces, because most minor injuries heal without noticeable scar formation.

HISTOPATHOLOGY

The tissue changes are similar to those in aphthous minor. The inflammation extends deep into the underlying connective tissue, and perivascular infiltrates of lym-

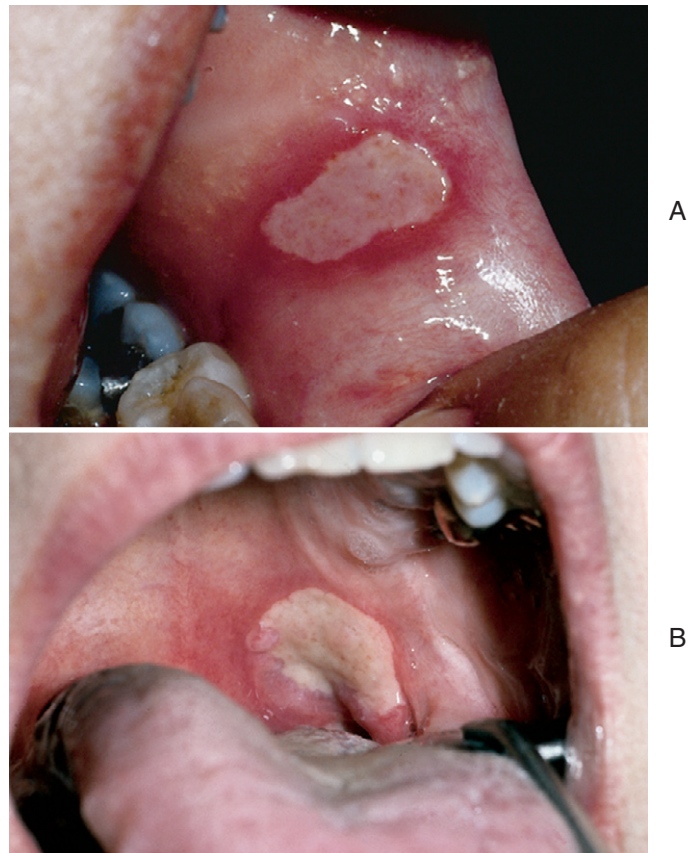


FIGURE 8-3

Recurrent aphthous major. Large shallow ulcers of labial mucosa (A) and lateral soft palate (B). Lesions are painful and exhibit characteristic erythematous halo.

phocytes are a prominent finding. The surface of the ulcer is covered with a fibrinopurulent exudate over granulation tissue. The healing period for prolonged lesions differs from aphthous minor, because the connective tissue destruction is often more extensive, requiring replacement of large amounts of normal structures with scar tissue before complete healing.

TREATMENT

The management of aphthous major usually requires an emphasis on the combined use of short-term systemic and topical steroids. Antimicrobial rinses may be required as an adjunct to reduce or prevent secondary infection. Use of topical anesthetic is sometimes necessary to allow adequate nutritional intake. If lesions are in the posterior aspect of the mouth, topical anesthetics must be judiciously administered, because extension of the anesthetic effect to the epiglottitis could result in serious consequences to the patient while eating.

HERPETIFORM ULCERS

HERPETIFORM ULCERS: *Rare, multiple, small, diffuse, painful, superficial ulcers with episodes of long duration that occur on both gland-bearing and keratinized mucosal surfaces.*

Herpetiform ulcers are the least common form of RAS, and the form most often misdiagnosed. They are frequently mistaken for primary herpes simplex infections, which they closely resemble clinically (hence their name).

CLINICAL FEATURES

Patients with herpetiform ulcers have prolonged episodes of widely distributed intraoral lesions of small (3 to 6 mm in diameter), shallow, and crateriform ulcers (Figure 8-4). An episode may last for weeks to months, and some patients may experience lesions nearly continuously for several years. During prolonged attacks, individual lesions heal while new ones continually reappear. They are seldom found in patients in their late teens, as is common with aphthous minor, or in children, as is common with primary herpetic stomatitis, the condition that the ulcers clinically resemble. Although most lesions are almost exclusively found on the gland-bearing mucosa, these lesions may also occur on some keratinizing surfaces. Because the presence of lesions on the keratinizing mucosal surfaces is common in primary herpes infection, herpetiform ulcers are often misdiagnosed as a herpes infection. Pain that is more excessive than is warranted by the size of the lesions is a prominent feature of this condition.

Because of the ease of confusing herpetiform aphthous lesions with primary herpetic stomatitis, laboratory



FIGURE 8-4

Herpetiform (aphthous) ulcers. Clusters of small shallow aphthous ulcers of the labial mucosa that resemble lesions of a herpes simplex infection.

tests are often necessary to rule out a viral cause. Cytology smears do not show the cytopathic effects or the multinucleated cells found in the epithelium of viral infections. Viral cultures, immunofluorescence for the herpes antigen, and ultrastructural examination for the presence of the virus are negative.

HISTOPATHOLOGY

The microscopic features of individual lesions are identical to lesions of aphthous minor. Lesions tend to be shallow with little connective tissue destruction; thus scarring does not occur.

TREATMENT

The use of systemic steroids is often the only effective method of managing herpetiform ulcers. It may require the prolonged use of low-dose steroid treatment to prevent rapid recurrence of lesions during a prolonged attack. Because of the large number of widely dispersed lesions, treatment with topical steroids or chemical cauterizations is often not practical or effective. Some patients have obtained temporary relief with oral rinses of tetracycline. In other patients, this form of management is of little value.

BEHÇET SYNDROME

BEHÇET SYNDROME: *A multisystem disease of uncertain pathogenesis, consisting of multiple oral, anogenital, and ocular aphthouslike lesions; frequently with arthralgia and associated central nervous system (CNS) involvement.*

Behçet syndrome is an uncommon complex multisystem condition that is diagnosed by means of clinical criteria. It lacks the specific diagnostic features or laboratory test results that make its identification easy. Therefore diagnosis depends on the grouping together of sufficient clinical manifestations for the clinician to be convinced of the diagnosis. In 1989 the International Study Group for Behçet Syndrome proposed criteria that classified the condition as one of the vasculitis syndromes. The group described the main features as consisting of oral and genital aphthae, pustular vasculitic cutaneous lesions, and ocular and GI vasculitic lesions. At present, the cause of Behçet syndrome is unknown. Immune factors, infectious agents, and immune effector mechanisms have been implicated. The main systemic pathologic process is vascular inflammation with a tendency for venous thrombus. In 50% of the patients, circulating autoantibodies to oral mucous membrane are found. Familial occurrences have been reported. It appears more commonly in Japan and eastern Mediterranean countries where it is linked to those with the HLA-B5 alloantigen. It affects mainly young adults, with men being more severely afflicted than women.

CLINICAL FEATURES

The most prominent and consistent feature of Behçet syndrome is the presence of intraoral ulcers identical to aphthous minor ulcers. Similar lesions are usually present in the anogenital area. Patients consistently have ocular symptoms of varying degrees of severity, ranging from photophobia to uveitis. The presence of oral, anogenital, and ocular aphthouslike lesions is usually sufficient to make the diagnosis of Behçet syndrome. Other common features of the syndrome include arthralgia, mainly of the ankles and knees, thrombophlebitis, CNS involvement, and macular and pustular skin lesions. In some, the skin is hypersensitive to minor scratches or other irritations. An abnormally intense inflammatory reaction to an intradermal injection of a small amount of saline (pathergy test) may be a useful diagnostic aid.

HISTOPATHOLOGY

The tissue changes of ulcerative lesions are similar to those of aphthous minor, except that the vascular component is more prominent. Blood vessel walls exhibit infiltrates of inflammatory cells, resulting in a severe vasculitis that appears to destroy the vessel walls.

TREATMENT

Although the condition may undergo spontaneous remission for prolonged periods, in most patients the use of topical and systemic steroids is necessary to achieve relief of symptoms and to prevent serious ocular damage during an episode. Colchicine, dapsone, thalidomide, and other immunosuppressive agents have been effectively used in severe cases to reduce the amount of steroid therapy to the patient. Early use of azathioprine has been shown to effectively aid the long-term prognosis.

MUCOSAL AND SKIN CONDITIONS

LICHEN PLANUS

LICHEN PLANUS: A skin disease common within the oral cavity, where it appears as either white reticular, plaque, or erosive lesions with a prominent T-lymphocyte response in the immediate underlying connective tissue.

Oral lichen planus (OLP) is a relatively common inflammatory disease affecting between 0.5% and 2.2% of the population. Lesions occur on both cutaneous and oral surfaces (40%), cutaneous surfaces only (35%), and mucosal surfaces only (25%). In contrast with cutaneous lichen planus (LP), in which the clinical course is often mild and resolves within 2 years, oral LP tends to follow a more chronic course, often punctuated by acute exacerbations. Furthermore, although distinct clinical subtypes

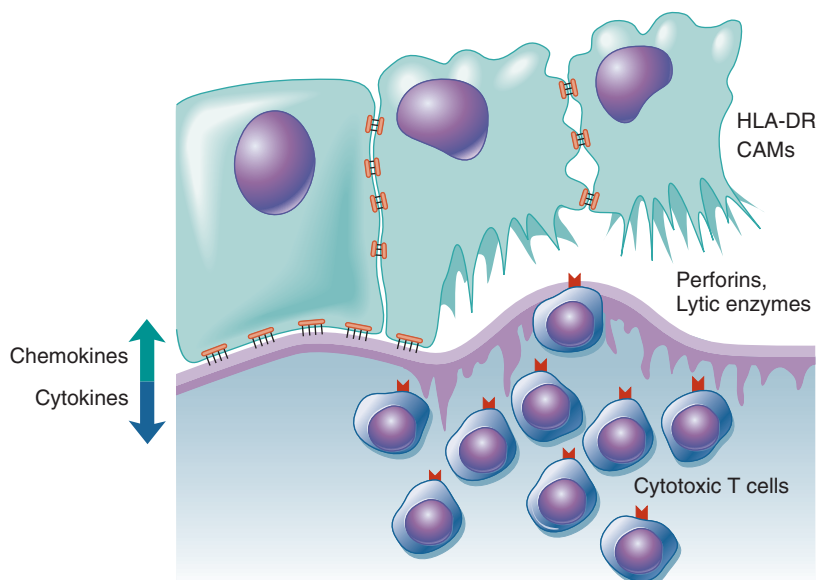
such as reticular, atrophic, hypertrophic, and erosive forms are well recognized, more than one clinical subtype may be seen at a time.

At present, the causative factors initiating LP are still unknown. In some countries a correlation with hepatitis C has been found. To date, this has not been the North American experience. After much research into the immune and pathologic mechanisms that underlie OLP, it is possible to piece together part of a complex picture of the disease process. There appears to be a mechanism for activating the regional cellular immune response and another for the T-lymphocyte response that eventuates in the destruction of the deep-layered keratinocytes. The initiating factors of the first mechanism are still unknown but are thought to be an external antigen that penetrates the superficial cells to stimulate intraepithelial dendritic Langerhans cells to activate the regional cellular immune response. The stimulated CD4 and CD8 T-lymphocytes express integrin ligands and leukocyte function-associated antigen-1 (LFA-1) and are guided out of the submucosal vessels toward the basement membrane by keratinocyte expressing intracellular adhesion molecules (ICAM) under the influence of epithelial chemotactic factors. These keratinocytes appear also to be able to express major histocompatibility complex II molecules (MHC-2) that bind T-lymphocyte receptor molecules, releasing cytokines including the perforins that trigger apoptosis of the basilar and parabasilar epithelial cells (Figure 8-5).

There have been sporadic reports in the literature that LP may be responsible for the subsequent development of squamous cell carcinoma. Although the documentation of many of the reported cases is not always complete, transformation to malignancy is rare and estimated to occur in 0.4% to 2% of LP patients when lesions persist for 5 or more years. Because many dysplasias have a dense infiltrate of lymphocytes in the same location as is found in LP, it is possible that some cases thought to be LP preceding a malignancy on a histologic basis were, in reality, early cases of epithelial dysplasia. At present, cases of epithelial dysplasia with an LP-like infiltrate of lymphocytes have been designated as *lichenoid dysplasia*. Another consideration when evaluating cases of transformed LP is that reports indicate many lesions are located on the lateral borders of the tongue, areas that are highly susceptible to the development of carcinoma, regardless of prior disease processes. Some experienced clinicians believe that mucosa subjected to prolonged LP becomes more susceptible to a secondary initiating carcinogen than do adjacent nonstimulated areas. However, the occasional well-documented case of squamous cell carcinoma is seen in which it arises in an uncommon location where there has been long-term presence of LP. To date, no direct cause-and-effect relationship has been established.

FIGURE 8-5

Lichen planus. An undefined antigenic stimulus resides in the epithelium and instigates a CD8 cytotoxic T-cell response with release of lymphocyte and keratinocyte cytokines and chemokines that activate T cells and promote chemotaxis into the epithelium. When excess cytotoxic T cells infiltrate the basilar epithelium, perforins are released and cause basal cell lysis and progression of the disease to an erosive and desquamative process.

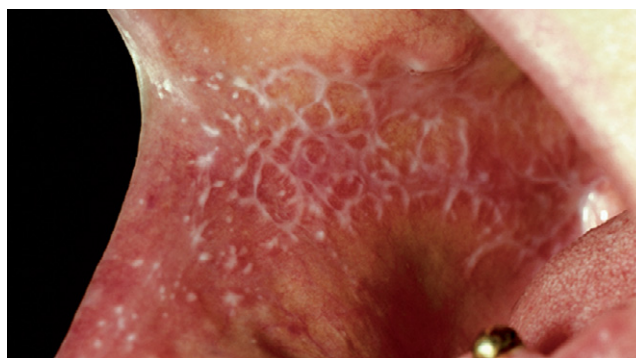


CLINICAL FEATURES

LP has a wide range of clinical appearances that correlate closely with the severity of the disease process. Three distinct clinical presentations exist: (1) reticular, (2) erosive, and (3) plaque. It is common for patients to have a combination of the reticular and erosive forms. Plaque LP usually occurs alone and resembles most other forms of leukoplakia. Oral LP occurs in men and women between the ages of 30 and 70; children and adolescents are rarely affected.

Reticular LP of the mucous membranes is easily diagnosed because of its unique and distinctive pattern. It consists of raised, thin, white lines that connect in arcuate patterns, producing a lacework or reticular appearance against an erythematous background (Figure 8-6). The white lines are referred to as *Wickham's striae*. Patients with reticular LP seldom have symptoms and are usually unaware of their condition unless their dentist or dental hygienist notices it. A lesion may become sensitive if an area becomes atrophic or erosive because of an intensification of the condition. Reticular LP most commonly occurs on the buccal mucosa and the buccal vestibule; the tongue and gingiva are the next most common locations. It is unusual for lesions to occur only on the hard or soft palates without involving most of the other oral mucosal surfaces. A feature of reticular LP is that it is usually bilateral.

Erosive LP appears as a mixture of erythematous and white pseudomembranous areas (Figure 8-7). Frequently the junction between the erosive areas and the normal mucosa exhibits a faint whitish tinge that resembles radiating striae. The whitish peripheral zone is most often present on the buccal mucosa and vestibule areas. Patients with this form of LP complain of a sore mouth that is sensitive to hot and cold temperatures,

**FIGURE 8-6**

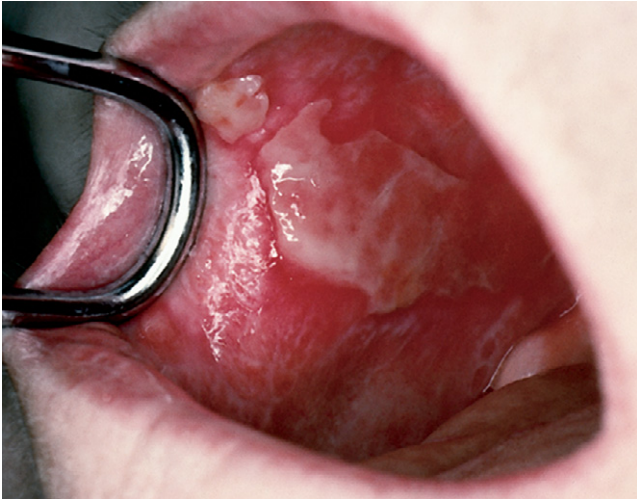
Lichen planus. Clinical appearance of the lacework pattern of the reticular form of the disease.

spicy foods, and alcoholic beverages. When erosive LP is severe, most patients seek a bland liquid diet.

During examination, touching the areas produces pain and bleeding. In most cases it is not possible to make the correct diagnosis without a biopsy of the perilesional tissue.

The clinical appearance of the erosive LP is difficult to differentiate from candidiasis, mucous membrane pemphigoid (MMP), pemphigus vulgaris (PV), or discoid lupus erythematosus (DLE). After prolonged involvement with erosive LP, areas of hyperpigmentation (melanosis) will occasionally occur on the mucosa in the healed areas.

Plaque LP appears as a white raised or flattened area on the oral mucous membranes and is indistinguishable from other focal leukoplakias (Figure 8-8). The most common location is on the tongue, where it produces irregular, white, smooth areas and raised plaques.

**FIGURE 8-7**

Lichen planus. Clinical appearance of the symptomatic erosive form of the disease on the buccal mucosa, exhibiting a large area of erosion against an erythematous background.

**FIGURE 8-8**

Lichen planus. Plaque form of LP on the buccal mucosa.

Often more than one area is involved, particularly on the dorsal surface of the tongue.

Other clinical forms of LP have been occasionally described that appear to be either a variant of plaque LP or are transient in nature. One of these is atrophic LP. The clinical appearance of atrophic LP is identical to the erythematous background of the reticular form and may be part of the transitional stage from reticular to erosive LP. Atrophic LP is most common on the gingiva and buccal mucosa. A rare form of LP, consisting of large bullae ranging in size from 4 mm to 2 cm, is bullous LP. The bullae are of brief duration and rupture almost immediately; with the loss of the separated epithelium, the underlying connective tissue is exposed and the lesion becomes an erosive LP. Reports indicate that bullous lesions occur primarily on the posterior buccal mucosa.

Patients with a depletion of immunocompetent cells and who require infusion of competent cells in the form of bone marrow transplants or transfusions often develop a condition referred to as *graft-versus-host disease* (GVHD). This condition develops when the acquired immunocompetent T lymphocytes attack the host cells of patients who are not sufficiently histocompatible. This is the opposite of what occurs when a healthy patient receives an incompatible graft, and the patient's immune system attempts to reject the graft. Part of the host cell response to GVHD is a skin and mucous membrane reaction that is histologically identical to LP. The oral changes may be the first indication that a serious problem exists that can be fatal if not treated. Death frequently results if the immunodeficient patient has received a large transfusion of improperly prepared blood in which the lymphocytes have not been removed.

**FIGURE 8-9**

Lichen planus. Papular skin lesions distributed in a linear pattern on the flexor surface of the wrist.

LP of the skin assumes a very different appearance than do lesions of the mucous membranes. Cutaneous LP is purported to occur in 35% to 44% of patients who seek medical attention for oral lesions. On the skin, lesions appear as clusters or diffuse areas of raised purplish papules with white keratotic caps. Because lesions are usually itchy, patients commonly produce linear excoriations that result in the development of a linear pattern of additional lesions along the scratch marks (Figure 8-9). The development of skin lesions extending along areas of injury or irritation is referred to as the *Koebner phenomenon*. This characteristic feature of LP may explain the increased size and intensity of oral lesions in areas prone to chronic irritation from teeth and toothbrushing. These areas are

commonly on the buccal mucosa along the occlusal line and commissure, the lateral borders of the tongue, and the marginal gingiva. Cutaneous lesions can occur on almost any part of the body (Figure 8-10), including the scalp and nail beds, but they are most prevalent on the upper trunk, the flexor surfaces of the arms and legs, and the genitalia.

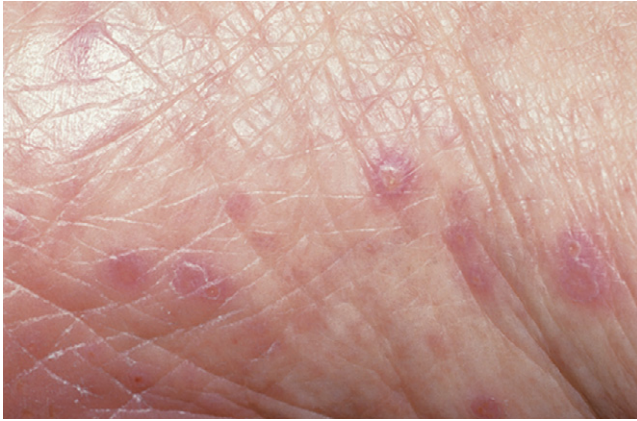


FIGURE 8-10
Lichen planus. Papular lesions on the skin of the sole of the foot.

DIAGNOSIS

LP is often diagnosed based on clinical information only, especially when reticular LP is present with its characteristic Wickham's striae in a lacework or annular pattern against an erythematous background. The erosive and plaque variants of LP always require laboratory evaluation, because they can clinically resemble a number of other mucosal lesions including malignancy. Incisional biopsy is required for histologic and direct immunofluorescent examinations.

HISTOPATHOLOGY

The histologic features vary with the clinical types of LP. Reticular LP consists of focal areas of epithelial hyperplasia in which the surface contains a thick layer of orthokeratin or parakeratin. The spinous cell layer may be thickened (acanthosis) with shortened and pointed ("saw-tooth") rete pegs. The thickened areas are seen clinically as Wickham's striae. Between these areas the epithelium is thinned (atrophic), with loss of rete peg formation. The adjacent underlying connective tissue contains a narrow, dense accumulation of T lymphocytes that transgresses the basement membrane and is observed in the basilar and parabasilar cell layers of the epithelium (Figure 8-11, A).

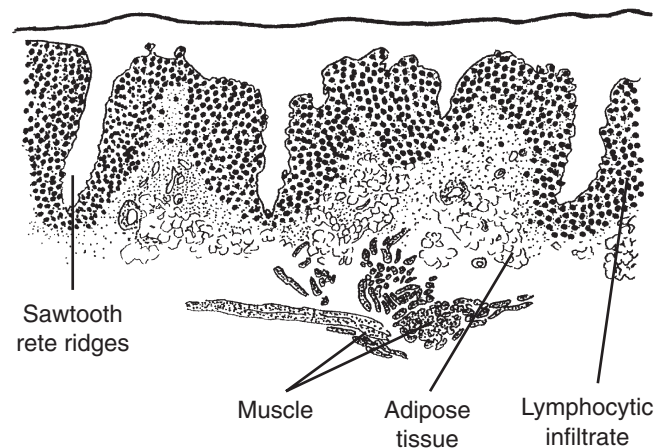
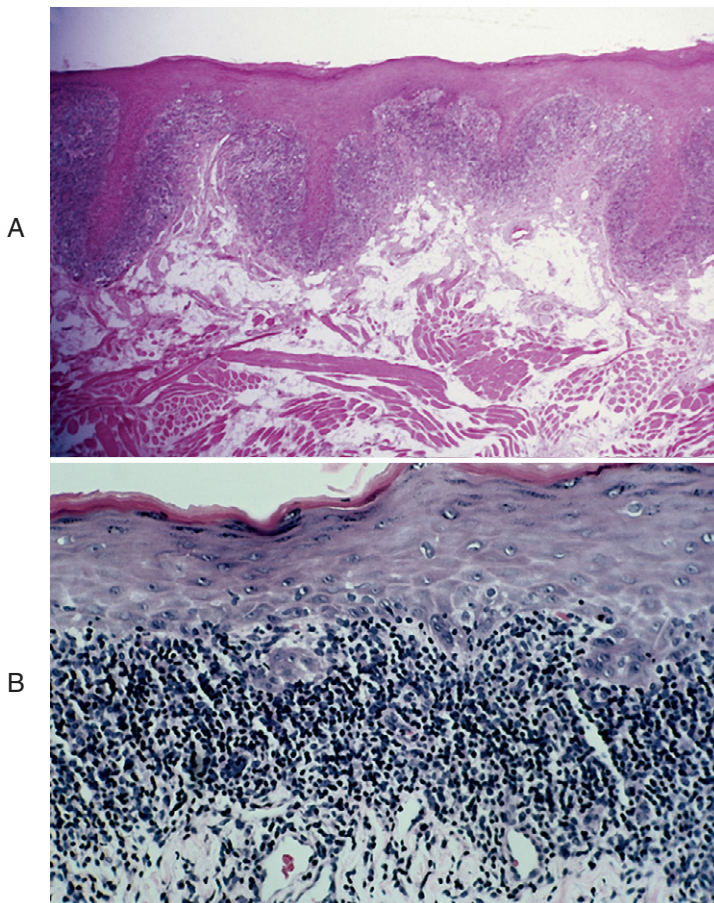


FIGURE 8-11
Lichen planus. Microscopic features demonstrating the characteristic narrow dense band of T lymphocytes in the immediately adjacent connective tissue of reticular LP (**A**) and atrophic and erosive LP (**B**).



Within the epithelium, rounded or ovoid amorphous eosinophilic bodies, referred to as *Civatte bodies*, are sometimes present. They are thought to represent apoptotic (dead) keratinocytes or other necrotic epithelial components that are transported to the connective tissue for phagocytosis. Immunofluorescent examination demonstrates a deposit of fibrinogen along the basement membrane, with vertical extensions into the immediate underlying connective tissue. Immunohistochemistry using the antibody to the S-100 protein indicates an increase in the Langerhans cells in the midlayers of the epithelium. Occasionally, lymphoid follicles will be found deeper in the connective tissue in patients with long-term disease.

Erosive LP exhibits an extensively thinned epithelium with areas of complete loss of rete peg formation and a dense infiltrate of T lymphocytes that obscures the basement membrane and extends well into the middle and upper levels of the epithelium. Liquefaction of the basement membrane and vacuolization and destruction of the basal cells is present in most areas (Figure 8-11, B). Occasionally, subepithelial separation will be present. Often, the epithelium is lost, exposing the underlying connective tissue. The lymphocytes are confined to a narrow zone in the upper layers of the connective tissue.

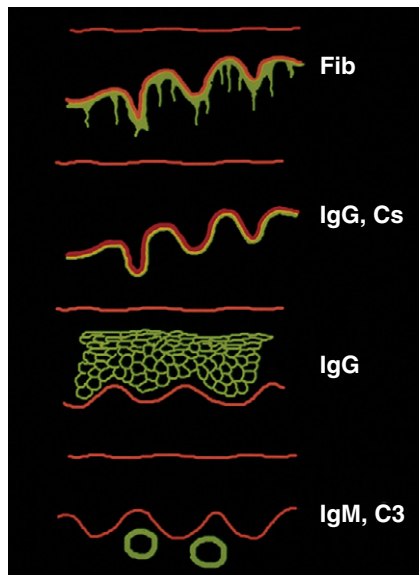


FIGURE 8-12

Lichen planus. Immunofluorescent patterns and antibodies of the common autoimmune conditions found within the oral cavity. From top to bottom: LP, *fibrinogen* in a shaggy pattern at the basement membrane; mucous membrane pemphigoid, *IgG* and *C3* in a smooth pattern at the basement membrane; pemphigus vulgaris, *IgG* in a “fishnet” pattern outlining cells of the epithelium; erythema multiforme, *IgM* and *C3* in a perivascular pattern within the deeper connective tissue.

Plaque LP resembles the histology of the striae of reticular LP but without the intermittent atrophic areas of the epithelium. It consists of generalized hyperorthokeratosis or hyperparakeratosis combined with acanthosis. There may be loss of rete pegs at the epithelial and connective tissue interface or alteration of their shape into a “saw-tooth” pattern. The basement membrane is noticeably thickened. The band of T lymphocytes present in the superficial connective tissue is less dense than in reticular LP, with only occasional cells found in the lower levels of the epithelium.

The tissue diagnosis of LP can often be difficult but may be greatly aided by the use of immunofluorescence (Figure 8-12). All forms of LP will be negative for *IgG*, *IgM*, and *IgA* antibodies but positive for fibrinogen (Figure 8-13).

TREATMENT

The management of OLP varies widely, both among patients and fluctuations in disease activity. After diagnosis most clinicians do not think it necessary to treat small areas of the reticular or plaque type of LP unless they become symptomatic, persistent, or widespread. The more severe form of LP, erosive LP, does need to be treated and usually responds well to the use of topical or systemic steroids, or both. The specific type of medication chosen depends upon the individual case. In severe and diffuse afflictions, an initial high dose of prednisone gradually tapered over 1 week or the use of alternate-day therapy is commonly used. Both treatments are adrenal sparing

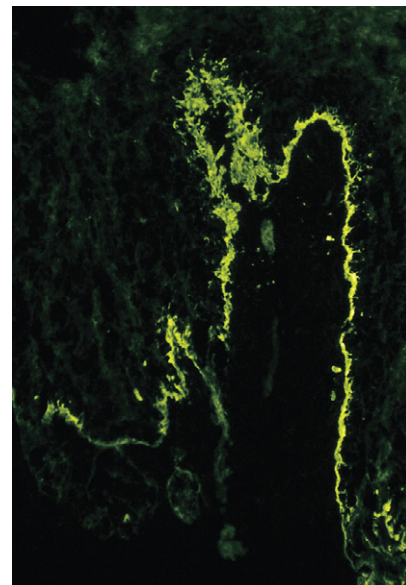


FIGURE 8-13

Lichen planus. Photomicrograph of immunofluorescent pattern of linear deposit of fibrinogen at the basement membrane.

but may only be used if the patient is not diabetic, hypertensive, severely osteoporotic, or suffering from GI ulcers or glaucoma. In compromised patients, lower doses combined with azathioprine may be effective. In milder forms of the disease, topical application of a fluorinated steroid such as fluocinonide, clobetasol, or halobetasol applied three to four times a day may be effective. In more resistant cases a combination of a systemic steroid and a locally administered topical steroid may be used.

LICHENOID REACTIONS

LICHENOID REACTIONS: *The presence of lesions resembling erosive lichen planus, mainly on the buccal mucosa; associated with the ingestion of some categories of medications and presence of other exogenous materials in the oral cavity.*

The prevalence of oral lichenoid reactions is increasing, because clinicians recognize that the entity may have a different cause than traditional forms of LP. The increased occurrence may be the result of the introduction of new categories of medications that have a greater tendency to produce lichenoid reactions as a side effect in individuals who are prone to this condition. The histologic and immunologic changes caused by medications are not different from the reactions caused by the usual form of LP, occasional amalgam and gold contact lesions, and the LP-like eruptions in patients with GVHD. On occasion, these lichenoid drug eruptions may show some microscopic features characteristic of oral discoid lupus erythematosus. The drug categories commonly associated with lichenoid reactions are systemically administered antibiotics, antihypertensives, gold compounds, diuretics, antimalarials, and nonsteroidal antiinflammatory medications (Box 8-1).

CLINICAL FEATURES

Within the oral cavity, lesions are primarily located on the posterior buccal mucosa. Lesions are usually painful and exhibit a central erythematous area of erosion with a surrounding zone of radiating striae that gradually fade (sunburst appearance) (Figure 8-14).

BOX 8-1

Major Categories of Medications Associated with Lichenoid Drug Reactions

- Antibiotics
- Antihypertensives
- Antimalarials
- Diuretics
- Gold compounds
- Nonsteroidal antiinflammatories

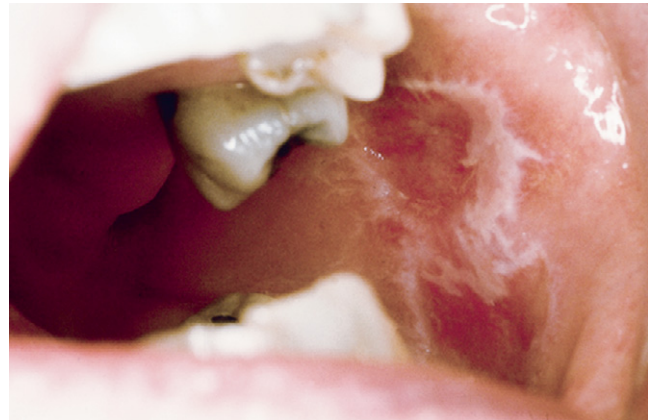


FIGURE 8-14

Lichenoid drug reaction. Clinical lesion on the buccal mucosa with central erythematous area and surrounding radiating white striae.

HISTOPATHOLOGY

The tissue exhibits changes that are identical to those seen in LP. The diagnosis of lichenoid drug reaction is usually made when the tissue report indicates that the lesion is consistent with LP and disappears after the offending medication is withdrawn.

TREATMENT

To provide more than temporary relief, treatment with the usual topical or systemic steroids must be combined with cessation or reduction in the dose of the offending medication.

MUCOUS MEMBRANE PEMPHIGOID

MUCOUS MEMBRANE PEMPHIGOID: *A desquamating condition of mucous membranes in which the autoimmune reaction occurs at the level of the basement membrane and commonly affects the gingiva before extending to other mucosal locations.*

The term *pemphigoid* is commonly used to indicate a desquamating or blistering disease in which epithelial separation takes place at the level of the basement membrane. Anchoring complexes are specialized focal attachment sites within the basement membrane zone (BMZ) and play an important role in the adhesion of the mucosal epithelium to the underlying connective tissue. Structural weakness that may be caused by the binding of autoantibodies to components of the anchoring complex or by aberrant expression of these components as a result of genetic defects can lead to submucosal blisters or separation.

In mucous membrane pemphigoid (MMP), the destruction involves components of the *hemidesmosome*—a dermal and epidermal complex composed of complex molecules that link the cytoskeleton of the epithelial

basal cell to structures within the underlying connective tissue. Three similar disease processes have been associated with destruction of the anchoring fibrils of the mucous membranes: (1) MMP, (2) cicatricial pemphigoid (CP), and (3) bullous pemphigoid (BP). In 1999 the First International Consensus on Mucous Membrane Pemphigoid was held to assimilate current information on this somewhat complex disease process. MMP was deemed the name best suited for the overall disease process, because all variants usually had some component of mucous membrane involvement. In the recent past, the terms *MMP* and *CP* were used synonymously; however, this has changed based on long-term findings.

It has been suggested that patients with chronic lesions confined to the oral mucous membranes be referred to as having oral mucous membrane pemphigoid (OMMP), those with eye lesions with a tendency for scarring as having CP, and those occasional patients with one or more bullous lesions on the skin (commonly in the head and neck areas) as having BP. In patients with BP, 10% to 20% also have oral lesions. In descending order of incidence of site of involvement, the oral cavity is first, followed by ocular, nasal, nasopharynx, anogenital, skin, laryngeal, and esophageal sites.

In all locations the epithelium atrophies then separates from the connective tissue at the level of the basement membrane, leaving painful, irregular erosive areas. When it is restricted to the gingiva only, it is the most common disease entity of a diagnostic grouping of clinical lesions collectively referred to as *desquamative gingivitis*.

The pathogenesises of OMMP, CP, and BP are similar, as revealed by immunologic and biochemical studies. Nearly all patients with skin lesions of BP have circulating autoantibodies to the BP-1 antigen, a 230 kD protein that is located in the hemidesmosome plaque at the base of the basal keratinocyte adjacent to the basement membrane. Approximately 50% of patients also have antibodies to BP-2 antigen, a 180 kD protein that is part of the anchoring apparatus of the epithelium to the basement membrane. The autoantibody that combines with the BP-1 and BP-2 antigen is an IgG class antibody, which precipitates a complement (C3) reaction that produces the disease process leading to the breakdown of the adhesive factors that anchor the epithelium to the basement membrane and the connective tissue. It has been recently found that laminin 5 (epiligrin) and BP-2, the prominent anchoring filament and lamina densa components of hemidesmosomes, are the target antigens for autoantibodies in patients that show the clinical phenotype of CP. Other less often identified antigens are laminin 6, beta-4 integrin, 105 kD, and 168 kD antigens (Figure 8-15).

Immunofluorescence stains viewed on microscopic slides reveal the autoantibody and antigen reaction to IgG and C3 of OMMP, CP, and BP to be present in a smooth and linear deposit along the basement membrane. This is sufficiently specific to be used routinely

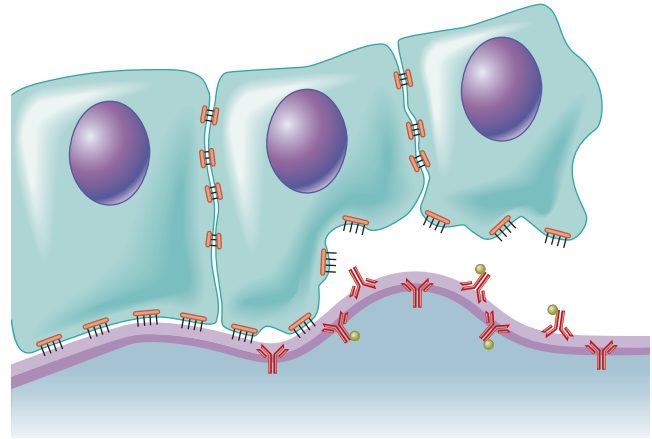


FIGURE 8-15

Mucous membrane pemphigoid. Autoantibodies are directed to protein targets located in the lamina lucida of the basement membrane. More than six different specific proteins have been identified in this disease. For this reason, MMP represents a phenotype with various biochemical immunopathologic targets. Both immunoglobulins and complement appear to initiate the basement membrane reaction with loss of adherence promulgating a subbasilar split.

for diagnostic purposes to differentiate MMP from PV and erosive LP, the other two oral lesions that may have similar clinical features.

CLINICAL FEATURES

In the oral cavity, OMMP lesions appear as atrophic erythematous patches (Figure 8-16), erosions, pseudomembranes, or collapsed blisters occurring most commonly on the attached gingiva and palatal mucosa. Less commonly, lesions are found on the tongue and buccal and labial mucosa. If they are not diagnosed and treated,



FIGURE 8-16

Mucous membrane pemphigoid. Gingiva containing patchy areas of erythema and atrophy with loss of normal stippling.

**FIGURE 8-17**

Mucous membrane pemphigoid. Gingiva exhibits loss of adhesion of epithelium to connective tissue.

**FIGURE 8-18**

Mucous membrane pemphigoid. Multiple diffuse areas of superficial erosions (*white*) against an erythematous background caused by mechanical forces of a denture on the fragile atrophic epithelium.

they may remain confined to the gingiva for long periods before extending to adjacent tissue. While lesions are on the gingiva, minor irritation from routine tooth brushing results in the separation of the epithelium from the connective tissue, blood-filled blisters or exposed connective tissue (desquamation) (Figure 8-17). Under a denture the tissue will appear as a generalized area of erythema and erosion (Figure 8-18). A clinical test that can be performed in this case consists of rubbing or pushing on the tissue with a blunt instrument or gauze to determine if a blister forms in the next 1 to 2 minutes. The production of a blister, or bulla, indicates a positive **Nikolsky sign**. A positive Nikolsky sign is not specific for MMP, because it may be present in other conditions that have defects in cell cohesion or basement membrane attachment. Often, patients will exhibit linear erosions along the free margins of the gingiva. These are the result of toothbrushing and flossing on the affected tissue.

Lesions generally progress to involve the buccal mucosa, palate, and floor of the mouth.

Extension into the nasopharynx, larynx, and esophagus has been observed. Genital lesions may be present

in a small number of the cases. Ocular MMP typically appears as conjunctival erosions and can result in scarring, symblepharon, ankyloblepharon, corneal neovascularization, and serious loss of visual acuity.

DIAGNOSIS

Evaluation of tissue specimens with light microscopy and direct immunofluorescence is necessary to separate MMP from all diseases with a positive Nikolsky sign. Of importance is the localization of the histologic site of tissue separation and the identification of the specific immunoglobulin profile at the site of the antigen and antibody reaction (Table 8-1). Because the targeted antigens in MMP are located in the plaque and lamina lucida zones, the splitting occurs at the level of the basement membrane.

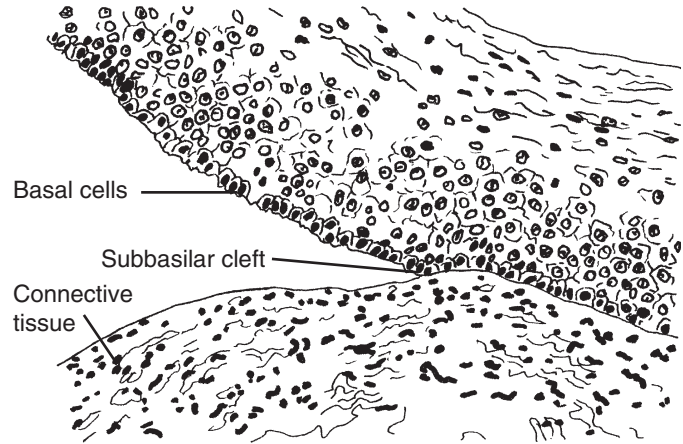
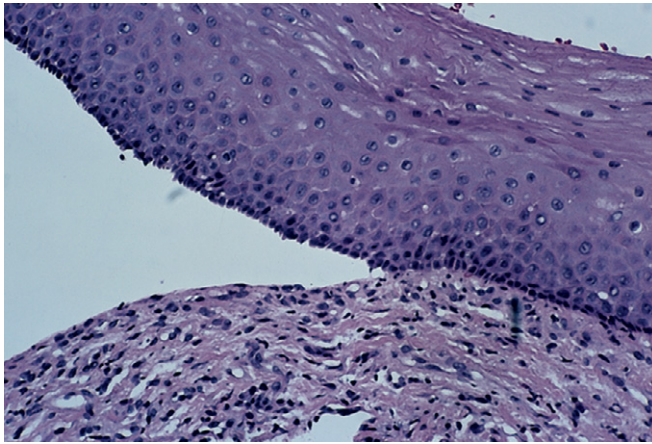
HISTOPATHOLOGY

The microscopic findings consist of a thinned epithelium that exhibits some attenuation of the rete pegs. Separation occurs at the basement membrane and leaves a connective tissue that is diffusely infiltrated with lymphocytes, some

Table 8-1 Tissue Diagnosis of Erosive Diseases of the Mucosa

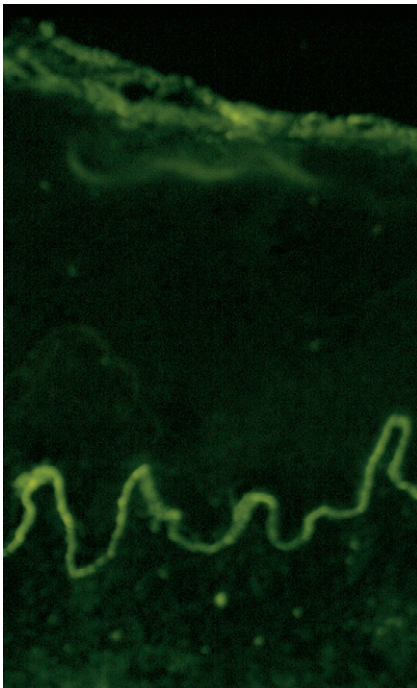
Disease	Location	Antigen	Direct IF
Erosive lichen planus (LP)	Basal cell/BM	Unknown	Fibrinogen, shaggy
Mucous membrane pemphigoid (MMP)	Hemidesmosome	BP-1,-2; Laminin 5	IgG, C3; smooth linear
Pemphigus vulgaris (PV)	Desmosomes	Desmoglein 3	IgG; fishnet pattern
Erythema multiforme (EM)	BVW/BM	Immune complexes	IgM, C3; perivascular

BM, Basement membrane; BVW, blood vessel wall; IF, immunofluorescence.

**FIGURE 8-19**

Mucous membrane pemphigoid. Photomicrograph of mucosa demonstrating lack of rete pegs and loss of adhesion of the epithelium with cleavage at the level of the basement membrane.

plasma cells, and occasional eosinophils (Figure 8-19). Vasodilatation is prominent in the underlying connective tissue. Immunofluorescence stains reveal a deposit of IgG antibody and C3 that follows the basement membrane in a smooth and linear pattern (Figure 8-20).

**FIGURE 8-20**

Mucous membrane pemphigoid. Immunofluorescence reveals a solid yellow-green line, indicating the presence of IgG antibody complexed to the antigen at the basement membrane.

TREATMENT

Patients are managed with a combination of systemic and topical steroids. Treatment of early lesions, particularly when confined to a few areas of the gingiva, will prevent progression of the disease and the necessity to treat serious eye, esophageal, or laryngeal afflictions with prolonged steroid, cyclophosphamide, or azathioprine therapy.

PEMPHIGUS VULGARIS

PEMPHIGUS VULGARIS: A desquamating condition of the oral mucosa and skin in which autoantibodies destroy antigenic components of the desmosomes of the intermediate cells, producing epithelial separation above the basal cell layer.

Pemphigus vulgaris (PV) and its less common variants are part of a group of dermatologic diseases characterized by epithelial desquamation caused by autoantibodies that attack the desmosome of the intercellular cohesive system. The loss of adhesion occurs between the cells located in the zone above the basal cell layer and results in suprabasilar bullous formation.

Other members of this disease group (pemphigus vegetans, pemphigus foliaceus, pemphigus erythematosus) represent milder forms and do not involve the oral cavity as extensively as PV. If untreated, PV can be a serious life-threatening disease, with a mortality rate of 60% to 90%. With aggressive immunosuppressive treatment, the patient death rate is about 5%. Mortality is due mostly to a combination of advanced age, infection, and other complications of high-dose steroid treatment.

Destruction of the adhesive factors of the suprabasilar spinous cells is referred to as *acantholysis*. Although this process is still not completely understood, some progress has been made. It is established that desmosomes and extracellular proteins accomplish intercellular adhesion of oral keratinocytes. Within the desmosomes a group of transmembrane glycoproteins, known as *desmogleins*, is found; desmogleins are part of the cadherin family of calcium-dependent adhesion molecules. In the early stages of PV the disease is confined primarily to mucous membranes and the patient's sera will contain circulating autoantibodies to desmoglein 3. This loss of cellular adhesion (acantholysis) and the loss of the epithelial layer above the basilar layer results in a suprabasilar split (Figure 8-21). When the disease becomes more severe, usually with associated skin lesions, the patient's sera will demonstrate autoantibodies to desmoglein 1 and 3. Titers of these autoantibodies correlate with disease activity and are useful in monitoring the progress of treatment.

CLINICAL FEATURES

PV is most prevalent in patients in the 40- to 60-year-old age group. It has a higher incidence in individuals of Mediterranean and Ashkenazic Jewish decent and

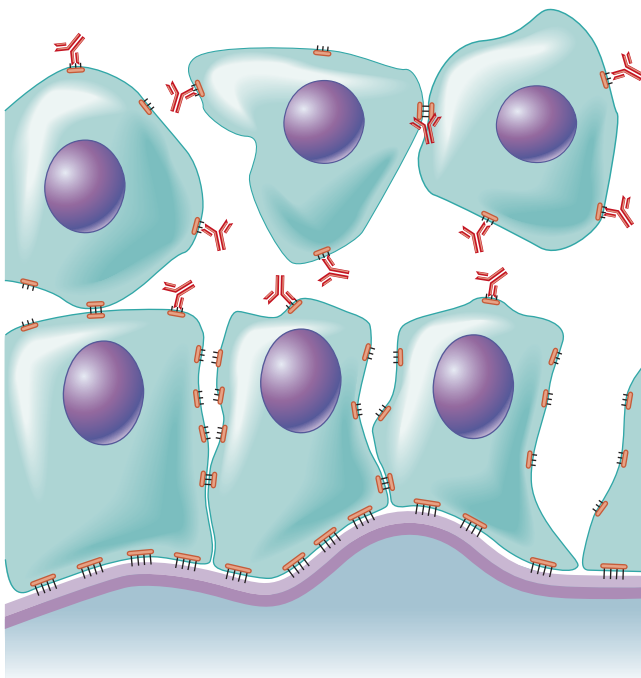


FIGURE 8-21

Pemphigus vulgaris. In this autoimmune disease, the desmosomal adhesion molecule, desmoglein 3 (a member of the cadherin family), becomes the antigenic target for an immunoglobulin-mediated reaction. When antibodies bind to the desmosomal complex, the junctions lose adherent contact, causing acantholysis. Desmoglein 3 is not present in the basilar hemidesmosome; hence the suprabasilar split.

those with specific histocompatibility antigens. The fact that certain ethnic groups are more prone to develop PV has lead to the theory that a genetic predisposition exists. The development of PV is thought to occur in predisposed patients with specific, major histocompatibility antigens on their skin and to mucosal keratinocytes. Drugs such as penicillamine, captopril, rifampin, penicillin, and phenobarbital have been associated with the development PV.

A particular form of PV occurs in association with a preexisting occult or confirmed malignancy called *paraneoplastic pemphigus vulgaris (PNP)*. These patients have particularly painful mucosal lesions and papulosquamous eruptions of the skin that progress to blisters. PNP occurs with some frequency in patients with non-Hodgkin lymphoma, chronic lymphocytic leukemia, Castleman disease, thymoma, and some spindle cell tumors.

PV mainly affects the skin of the torso. In nearly 50% of patients with cutaneous PV, the oral lesions precede the presence of skin lesions, often by as much as 1 year. Other mucous membranes such as the nasopharynx, esophagus, vagina, and cervix can also be involved. Bullae are commonly present on skin but are rare on the oral mucosa. Intraoral lesions are common on the soft palate, where they have a brief and usually undetected bullous stage. In this and most other intraoral locations the delicate surface layers are quickly lost, leaving the commonly observed erythematous area that is sensitive to hot and cold temperatures, spicy foods, and alcoholic beverages. The free margin of the gingiva (Figure 8-22), where chronic abrasion during toothbrushing is common, and the lateral borders of the tongue, where constant frictional activity occurs, will have larger and more intensely symptomatic



FIGURE 8-22

Pemphigus vulgaris. Gingiva demonstrating erosive lesion of the free margin of gingiva in an area commonly irritated during toothbrushing.

erosive lesions. Lesions are commonly found on the other mucosal surfaces of the mouth, particularly the soft palate (Figure 8-23) and buccal mucosa (Figure 8-24). Both skin and mucosal tissue will have a positive Nikolsky sign (Figure 8-25). On the skin the individual lesions are produced by briefly appearing blisters that collapse with the formation of a brittle reddish crust (scab) (Figure 8-26).

HISTOPATHOLOGY

The microscopic appearance of PV exhibits epithelium of normal thickness and normal rete peg formation. Mild inflammation is found in the underlying connective tissue. The basal cell layer is intact, but the cells of the suprabasilar layer are separated (acantholysis) and float freely in a fluid-filled intraepithelial

space (Figure 8-27). The cells lose their polygonal shape and become rounded with less cytoplasm visible around the nucleus. This gives the cells a malignant appearance when viewed on a cytology slide. These cells have been termed *Tzanck cells* and are a characteristic finding in the fluid in the area of epithelial separation in PV.

Immunofluorescence is a most valuable aid in the diagnosis of this condition. In the early stages of the disease, before the development of superbasilar separation and the presence of Tzanck cells, it may be the only means of diagnosis. It is also most helpful in detecting the disease on tissue biopsied from a perilesional location. The test reveals the presence of IgG antibody in a *fishnet* pattern because of its attachment to the periphery of the cells in the lower portion of the spinous layer



FIGURE 8-23
Pemphigus vulgaris. Multiple erosive lesions of the soft palate.



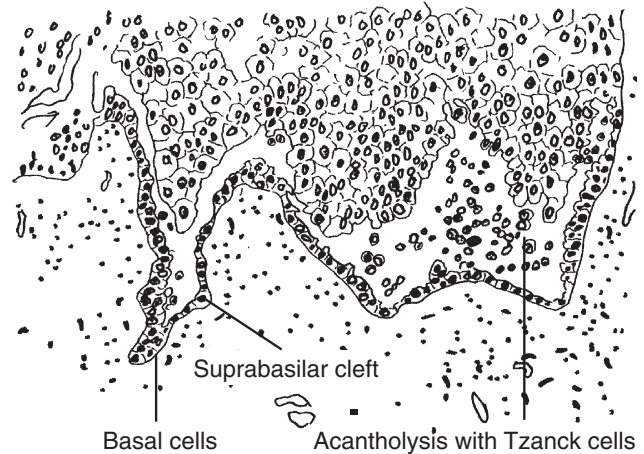
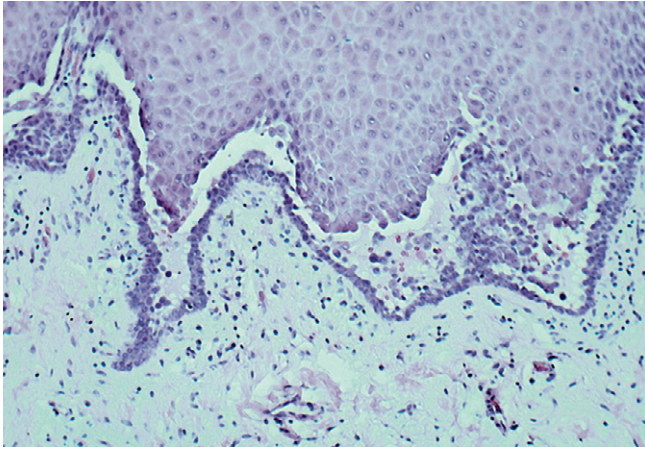
FIGURE 8-25
Pemphigus vulgaris. Blister formation (arrow) on normal-appearing gingiva after the movement of mirror handle under pressure indicative of positive Nikolsky sign.



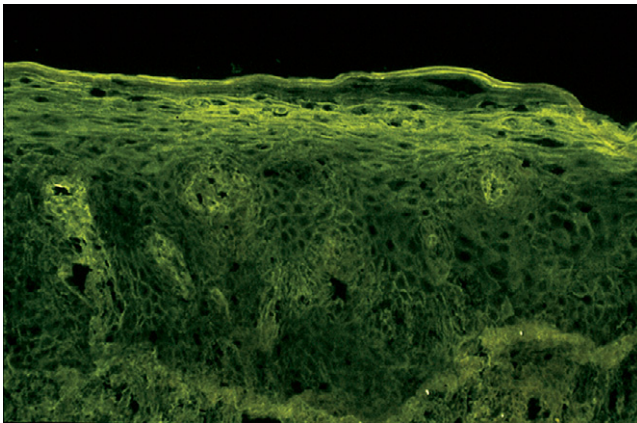
FIGURE 8-24
Pemphigus vulgaris. Erosive lesions of the posterior buccal mucosa.



FIGURE 8-26
Pemphigus vulgaris. Dry, crusted lesions on the skin.

**FIGURE 8-27**

Pemphigus vulgaris. Photomicrograph of epithelium exhibiting rete pegs and a zone of acantholysis above the basal cell layer. Spinous cells (Tzanck cells) are present and floating freely in the fluid-filled intraepithelial space.

**FIGURE 8-28**

Pemphigus vulgaris. Immunofluorescent pattern of the IgG antibody adherence to the desmosomal protein (desmoglein) located on the periphery of epithelial intermediate cells, producing a "fishnet" pattern of binding sites.

of the epithelium (Figure 8-28). Patients with PNP, in addition to having suprabasilar acantholysis, may exhibit a lichenoid tissue reaction. The immunoreactants, IgG and complement, can be observed within the desmosomes (targeting the desmoplakin proteins) and the BMZ.

TREATMENT

Treatment of PV is aggressive and requires a prolonged high dose of prednisolone in the range of 150 to 360 mg daily for 6 to 10 weeks. Because the side effects of prolonged high doses of steroids can be severe, doses are

often reduced after an initial period and are used in combination with other nonsteroid immunosuppressant drugs such as azathioprine. In most cases the condition eventually goes into remission and doses are greatly reduced or even withdrawn for a time. With modern combinations of medications, mortality rates have been drastically reduced.

EPIDERMOLYSIS BULLOSA

EPIDERMOLYSIS BULLOSA: A generalized desquamating condition of the skin and mucosa with associated scarring, contractures, and dental defects that occur in three main hereditary forms in children and one acquired form in adults.

Epidermolysis bullosa (EB) is an encompassing term for a large group of clinically similar disease processes that have in common the separation of the epithelium from the underlying connective tissue and the formation of large blisters that frequently result in extensive and often immobilizing scar formation. Four basic types exist, each of which have multiple subtypes. Three of the types have hereditary patterns, and one is acquired in later life. The acquired form is the only one thought to be solely of autoimmune origin. This simplified classification is based on a mixture of clinical and morphologic criteria.

The three major hereditary types of EB are (1) *epidermolysis bullosa simplex* (EBS), in which intraepithelial cleavage caused by cytolysis of the basal or intermediate cell layer (epidermolytic type) is found; (2) *junctional epidermolysis bullosa* (JEB), in which the cleavage is within the

basement membrane at the level of the anchoring filaments contained within the lamina lucida (lamina lucidolytic type); and (3) *dystrophic epidermolysis bullosa* (DEB), in which the cleavage takes place at the level of the type VII collagen-anchoring fibrils located beneath the lamina densa of the basement membrane where they extend into the dermis (dermolytic type). The diagnosis of the hereditary forms is best made with ultrastructural analysis, because the break in adhesion is not a result of an antigen and antibody reaction that can be detected with the usual immunofluorescent methods. Rather, the defect in epithelial adhesion is the result of congenitally absent or greatly reduced specific molecular factors (Figure 8-29). When electron microscopy is not available, panels of complex immunohistochemical stains using monoclonal antibodies against various constituents of the adhesive mechanism (immunofluorescence mapping) have been used to detect the absent factors (Table 8-2).

In the acquired type of EB, epidermolysis bullosa acquisita (EBA), detectable IgG (and sometimes IgA) autoantibodies to type VII collagen is found. In skin and

mucosa, anchoring fibrils composed of type VII collagen are important constituents of the complex adherence system of epithelium to dermis. They attach the lamina densa portion of the basement membrane to the underlying dermis. The attachment of autoantibodies to type VII collagen triggers a complement-mediated inflammatory reaction that can result in severe damage to the anchoring fibrils.

CLINICAL FEATURES

EB simplex is a mild form of EB with an autosomal dominant hereditary pattern. Lesions occur over sites of friction or trauma and usually involve the hands, feet, neck, and occasionally the knees and elbows. Teeth are not affected, but mild intraoral blisters are found. EBS appears during infancy, improving significantly by puberty.

JEB is a severe form of EB inherited as an autosomal recessive trait. It has previously been referred to as *EB letalis*, because some infants died within the first few months of life. Hemorrhagic blisters and loss of nails; large blisters of the face, trunk, and extremities; and generalized scarring and atrophy are common. Intraorally, large, fragile, hemorrhagic blisters of the palate and crusted, granular, hemorrhagic lesions are present in perioral and perinasal locations. Erupted teeth exhibit hypoplastic and severely pitted enamel that rapidly develops caries.

DEB occurs in both an autosomal dominant and a recessive form, with the recessive phenotype exhibiting the most severe forms of the disease. Lesions are apparent at birth and arise at sites of pressure such as the occiput, back, elbows, buttocks, and fingers. The bullae rupture, leaving painful ulcers that heal with large and deep scars that undergo contracture, leading to loss of mobility and clawlike hands (Figure 8-30). Fingernails and toenails are seldom present in adolescents and adults. There may be marked skin depigmentation and deficient hair. The teeth exhibit delayed eruption and enamel hypoplasia with rapid caries development. Blistering and scarring around the oral cavity result in a diminished opening, ankyloglossia, and loss of vestibular sulci with resultant difficulty in providing dental treatment. Attempts at maintaining normal oral hygiene generate more blister formation.

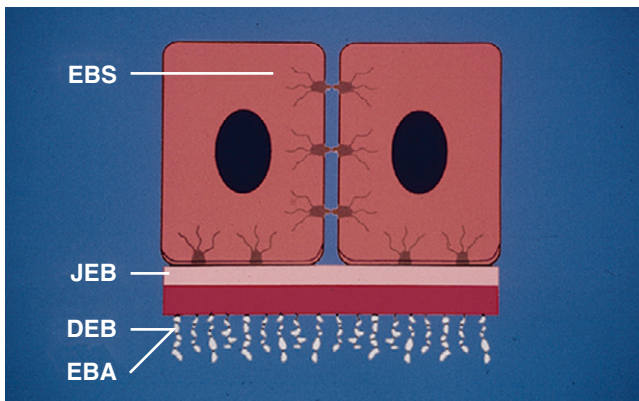


FIGURE 8-29

Epidermolysis bullosa. The various target sites where destruction of the components of epithelial adhesion occurs in the three major hereditary forms of epidermolysis bullosa simplex (EBS): (1) junctional epidermolysis bullosa (JEB); (2) dystrophic epidermolysis bullosa (DEB); and (3) the acquired form, epidermolysis bullosa acquisita (EBA).

Table 8-2 Major Categories of Epidermolysis Bullosa

Type	Genetic Pattern	Location of Separation	Defective Structure
HEREDITARY			
Simplex	Autosomal dominant	Intraepithelial	Linking proteins
Junctional	Autosomal recessive	Lamina lucida	Anchoring filaments
Dystrophic	Autosomal dominant/recessive	Sublamina densa	Type VII collagen
ACQUIRED			
Acquisita	None	Sublamina densa	Type VII collagen

**FIGURE 8-30**

Epidermolysis bullosa. Clawlike hands caused by deep scars and contractures of the soft tissue in a young patient with the recessive dystrophic form of EB.

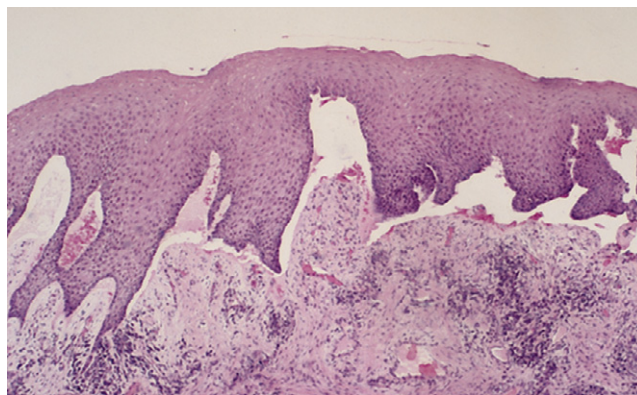
EBA is a nonhereditary form of EB that is manifested in adulthood. It has been associated with multiple myeloma, diabetes mellitus, amyloidosis, tuberculosis, and inflammatory bowel disease (particularly Crohn disease). The clinical findings closely resemble those of the less severe (autosomal dominant) forms of JEB, which is also a disease of the type VII anchoring fibrils. Patients with EBA experience trauma- or friction-induced blisters of the knees, elbows, and dorsal side of the hands and feet that heal with scars and milia. In some cases loss of nails and alopecia are common. Intraoral blisters are rare; when present they produce scarring and a diminished oral opening, leading to the deterioration of oral hygiene, high caries rate, and periodontal disease.

HISTOPATHOLOGY

The tissue of EBS exhibits a zone of cleavage above the basal cell layer. In the remaining types of EB the separation is subepithelial (Figure 8-31).

TREATMENT

The hereditary forms of EB are not immune- or inflammatory-mediated conditions. Instead they represent adhesive factors to that form; no specific treatment is available. Meticulous wound healing techniques, the prevention of infections, and the systemic use of phenytoin (Dilantin), the anticonvulsant also known to inhibit collagenase ac-

**FIGURE 8-31**

Epidermolysis bullosa. Photomicrograph of the acquired form, demonstrating the separation of the epidermis from the connective tissue at the level of the basement membrane.

tivity, have been helpful in ameliorating the morbidity of the disease. Although the acquired form (EBA) has an autoimmune basis, treatment with high doses of corticosteroids and immunosuppressant medications has not been substantially beneficial.

Maintenance of the patient's nutritional status is required in cases of restricted oral opening and esophageal strictures.

ERYTHEMA MULTIFORME

ERYTHEMA MULTIFORME: A widespread hypersensitivity reaction that occurs in mild and severe forms and produces tissue reactions centered on the superficial vessels of the skin and mucous membranes; usually occurs in patients as the result of an inciting agent.

Erythema multiforme (EM) is an inflammatory disease of immune origin that affects the skin and mucous membranes, with a wide spectrum of manifestations and varying degrees of severity. In most patients an inciting agent can be identified. Among the common precipitating factors are (1) infections such as herpes simplex, mycoplasma pneumonia, and histoplasmosis; (2) drugs (most commonly sulfas, penicillin, Dilantin, barbiturates, iodines, and salicylates); (3) some GI conditions (notably Crohn disease and ulcerative colitis); and (4) other conditions such as malignancy, radiation therapy, and recent vaccination (Box 8-2). Many cases exist in which a precipitating factor cannot be identified.

The pathogenesis of EM is mostly unknown. Research has identified circulating immune-related complexes that appear after patients have encountered some infections, particularly herpes and mycoplasma, and after allergic reactions to medications. The surface epithelium and the walls of blood vessels in the lamina

BOX 8-2**Common Precipitating Factors of Erythema Multiforme****INFECTIONS**

Herpes simplex
Mycoplasma pneumonia
Histoplasmosis

DRUGS

Sulfas
Penicillin
Dilantin
Barbiturates
Iodines
Salicylates

GASTROINTESTINAL CONDITIONS

Crohn disease
Ulcerative colitis

OTHERS

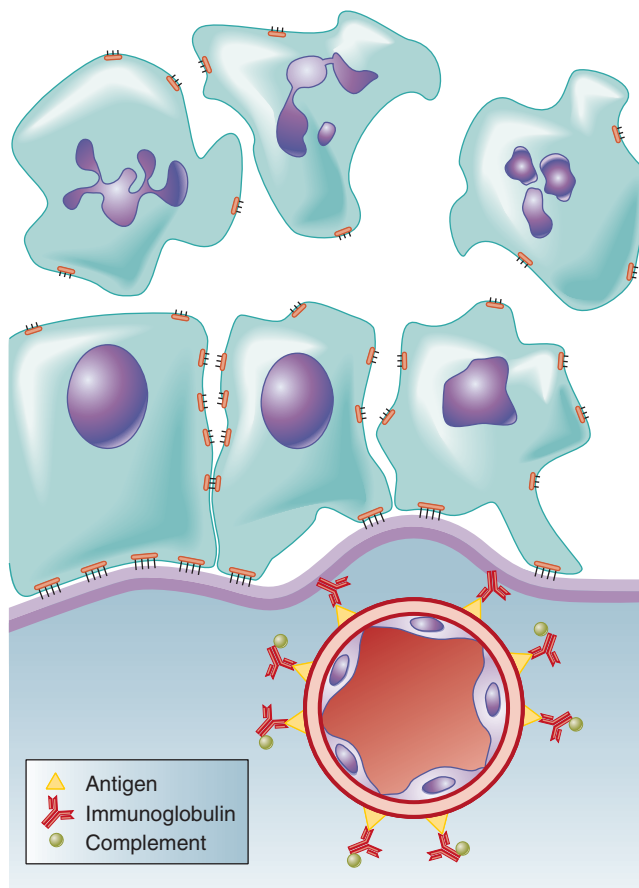
Malignancies
Radiation therapy
Vaccination

propria appear to be targeted. In some patients, antibodies form against an exogenous antigen and the complex circulates in the blood being filtered in the walls of blood vessels; there they cause a vasculitis, which results in small areas of thrombosis and ischemic necrosis. The resulting skin and mucosal reactions range from a mild erythema to widespread necrosis with sloughing of the epithelial layer, depending on the intensity of the immune response to the antigen (Figure 8-32).

CLINICAL FEATURES

EM appears in three clinical forms: (1) EM minor, (2) chronic EM minor, and (3) EM major. EM major has an unusually acute form of the condition found in young patients that is known as *Stevens-Johnson syndrome* (SJS). Another condition, *toxic epidermal necrolysis* (TEN), is an even more severe form of EM major that is associated with a high mortality rate. Both of these latter forms of the disease are characterized by large blister formation and sloughing of the epidermis. In SJS, widespread epidermal detachment involves 10% or less of the total body skin area; a transitional form of SJS and TEN is defined by an epidermal detachment between 10% and 30%, and TEN is defined by areas of detachment or blistering greater than 30%.

EM minor is a disease that primarily involves the skin; the oral mucosa is involved in only 25% of cases. Before the appearance of lesions, a 3- to 7-day prodromic period in which patients experience severe headache, fever, and malaise occurs. The prodromic period is followed by an emergence of focal or diffuse areas of erythema followed by the classic skin lesion that is variously referred to as a “target,” “bull’s eye,” or “iris” lesion (Figure 8-33). Each of the descriptive terms denotes the common appearance of a concentric erythematous patch that contains a peripheral thin zone of pallor and is surrounded by one or more additional thin,

**FIGURE 8-32**

Erythema multiforme. The immunopathogenesis of EM is linked to exogenous rather than endogenous antigen. Pharmacologic agents such as sulfa drugs or herpes virus antigens form circulating immune complexes that filter into vascular basement membranes in skin and mucosa. These components bind complement and initiate a vasculitis with thrombosis and ischemic necrosis of the overlying epithelium.

**FIGURE 8-33**

Erythema multiforme. Skin of a young patient exhibiting characteristic “target” lesions.

erythematous rings. In the early stages the center of the ring develops a raised papule or small bulla that collapses, producing a transient central erosion that quickly heals and returns to normal, which then produces the center of the “bull’s eye.” Individual “target” lesions range from a few millimeters to many centimeters and are distributed mostly on the flexor surfaces of the extremities; the trunk and facial surfaces are less frequently involved. Although the condition can occur in individuals of any age, young adults are most commonly involved. The condition is self-limiting, usually resolving in 2 to 3 weeks. Treatment sometimes helps to shorten this period. Recurrent episodes of the disease are not uncommon.

Chronic EM minor is the mildest form of EM. Skin lesions are smaller in size and of shorter duration and distribution than in the other forms. In chronic EM minor the patient may have lesions continually for 1 or more years. In these patients the appearance of the lesions is similar to that of a disseminated viral eruption (Figure 8-34). Individual lesions will disappear rather than developing into large “target” lesions.

Oral lesions in both forms of EM minor are similar, varying from focal erosions resembling aphthous ulcers to more diffuse areas of erythema or erosions that are painful to the patient (Figure 8-35). In general, the lesions are very nonspecific and require the presence of associated cutaneous lesions and a compatible history to make the diagnosis. Tissue examination is of little help but may be useful in ruling out other more histologically specific diseases.

EM major is an acute form of the disease with severe involvement of both the skin and mucous membranes. Although the typical “target” lesions found in other forms of EM will be present, large bullae of both the mu-

cous membranes and skin and occasionally a positive Nikolsky sign are characteristic of this severe form of the disease. The bullae quickly collapse, producing whitish pseudomembranes on the mucosa and dark-red, crusted lesions on the dry skin surfaces. These are particularly noteworthy on the lips (Figure 8-36) and eyes, because after sleeping, patients are often unable to open their eyes or part their lips because of the dry encrustations.

The incidence of SJS has been reported as one to three cases per million per year. The most extensive study of prior use of medications and the subsequent development of SJS or TEN mainly pointed to antibacterial sulfonamides, anticonvulsant agents, some nonsteroidal antiinflammatory drugs, and allopurinol.

Mortality rates of patients with SJS are reported as 5%. Mucosal lesions of SJS are usually extensive and involve the mouth, eyes, esophagus, and genitalia. The oral lesions are very painful, and eye lesions may lead to scarring and partial blindness.

TEN is considered an extremely severe form of EM major and is fatal in 30% to 35% of patients. Large sheets of skin become necrotic and slough, exposing



FIGURE 8-34

Erythema multiforme. Skin lesions of the chronic form of EM minor, demonstrating long-standing multiple small “target” lesions.



A



B

FIGURE 8-35

Erythema multiforme. A, Erosive lesions of the labial mucosa and gingiva. B, Diffuse area of superficial sloughing and focal erosions of the palate.

**FIGURE 8-36**

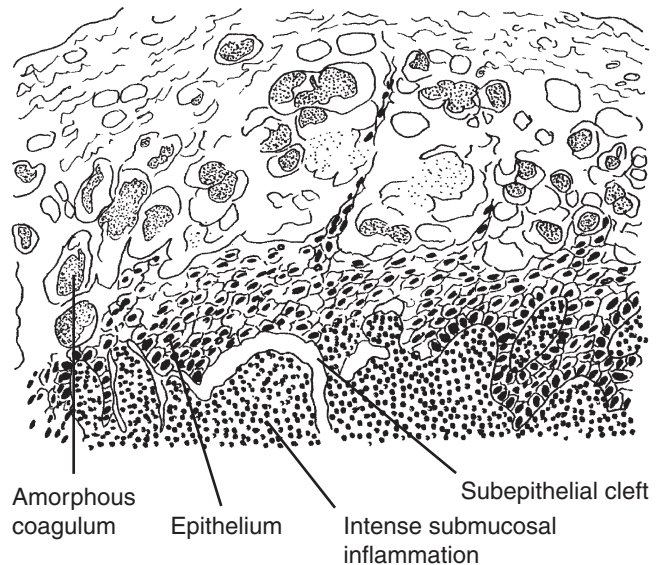
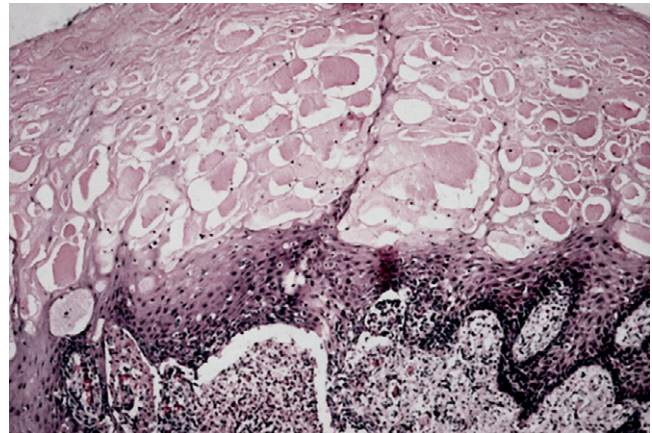
Erythema multiforme. Acute form of EM major (Stevens-Johnson syndrome [SJS]) in 2-year-old male, exhibiting characteristic "target" lesions of the skin and hemorrhagic encrustations of the lips.

denuded connective tissue that can result in massive loss of electrolytes and widespread infection. The skin areas clinically resemble severe burns caused by scalding water. Oral lesions in these patients are similar to the sloughing lesions found in SJS but are even more diffuse and widespread.

HISTOPATHOLOGY

The tissue changes of EM are variable, reflecting the wide spectrum of clinical presentations. The tissue changes in the milder forms of the disease are often described as nonspecific, but some consistent features have been described.

Intercellular and intracellular edema of the overlying epithelium with focal microvesicle formation is one of the more consistent findings. Sometimes the edema results in a pooling of an eosinophilic amorphous coagulum within the epithelium that has been described as *keratin mucopolysaccharide dystrophy* (Figure 8-37). Migration of both mononuclear and polymorphonuclear cells into all layers of the epithelium is common. In some cases, acanthosis and irregular elongation of rete pegs is present. A generalized diffuse infiltrate of mixed mononuclear cells of the upper portion of the lamina propria is common. Vasodilatation of blood vessels with marked connective tissue edema and a tendency for interstitial transudate pooling often results in large zones of separation at the basement membrane level. Immunofluorescent stains indicate that these zones are negative for antigen and antibody reactions. The perivascular infiltrate around

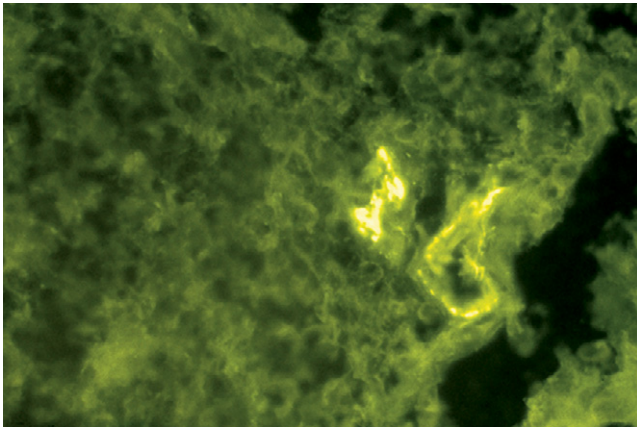
**FIGURE 8-37**

Erythema multiforme. Photomicrograph of mucosal tissue with extensive intraepithelial pooling of eosinophilic coagulum, separation of the epithelium from connective tissue (bullae formation), and intense chronic inflammatory cell infiltrates. (From Shklar G: Oral lesions of erythema multiforme: histologic and histochemical observations, *Arch Dermatol* 92:495, 1965.)

the blood vessels, deep in the lamina propria, and within the muscle layers is somewhat distinctive in mononuclear cells. Immunofluorescence testing reveals that the deep perivascularitis is positive for IgM and C3 (Figure 8-38). This finding, combined with the other tissue and clinical findings, is of considerable help in diagnosing EM.

TREATMENT

The success of the treatment depends on the clinician's ability to find and neutralize the initiating factor. If episodes follow herpes attacks, prophylactic management of the herpes with acyclovir has been effective. In

**FIGURE 8-38**

Erythema multiforme. Immunofluorescent pattern of the IgM antibody in a perivascular pattern deep within the connective tissue. A similar pattern occurs at the same site with C3.

most chronic cases finding and treating the inciting agent is not always possible. The condition is generally self-limiting, except in some chronic forms when, if left untreated, it could extend for years. Treatment in mild cases is symptomatic and consists of antihistamines, analgesics, and antipyretics combined with oral rinses of antihistamine or the use of a topical steroid. Systemic steroids are sometimes used, but research shows that little difference exists in the length of time in which lesions resolve with steroid administration when compared with other more conservative forms of treatment. For the best treatment, patients should be transferred to an intensive care unit or burn center. Prompt referral reduces risk of infection, mortality rate, and length of hospitalization. Thromboembolism is an important cause of morbidity; effective anticoagulation therapy with heparin is recommended for the duration of hospitalization.

LUPUS ERYTHEMATOSUS

LUPUS ERYTHEMATOSUS: A chronic inflammatory condition of the skin, connective tissue, and specific internal organs that has associated circulating autoantibodies to DNA and other nuclear and RNA proteins; circular whitish buccomucosal lesions and erythematous rashes of the sun-exposed skin are common.

Lupus erythematosus (LE) is a disease that has stricken over one million people worldwide. Females are afflicted nine times as often as males. It generally occurs during the childbearing ages, is insidious, and mimics various minor illnesses for many years before being diagnosed. Fifty years ago only 50% of LE patients survived longer than 10 years; however, at present, 95%

will exceed that mark. It occurs in three clinical forms that represent the severity and distribution of involvement. The mildest form, **discoid lupus erythematosus** (DLE), is chronic and confined to the sun-exposed skin of the face, scalp, and ears but also involves the oral mucosa. The intermediate form, **subacute cutaneous lupus erythematosus** (SCLE), is more widespread and affects the head and neck, the upper trunk, and the extensor surfaces of the arms. The severest form, **systemic lupus erythematosus** (SLE), primarily involves the organs, especially the kidneys. Rashes occur periodically on the upper trunk and face.

The pathogenesis of LE is still not fully understood but is considered to be multifactorial, triggered by a combination of genetic, environmental, and hormonal factors. The environmental factors are thought to be viral infection, ultraviolet (UV) light, and drugs. Ample evidence shows that the immune system becomes altered and is responsible for the deleterious changes that take place within the basal cells, basement membrane, collagen, and vascular tissue. Autoantibodies to nuclear DNA (antinuclear antibodies [ANAs]), ribonuclear protein antigens, and cytoplasmic and surface antigens are present in the blood. The serology also notes an increase in B-cell function and circulating autoantibodies that exhibit cross-reactivity with antigenic determinants of multiple tissues. One theory of pathogenesis is that the process is initiated by an increase in cell death of lymphocytes, releasing nucleosomes that act as foreign antigens stimulating B lymphocytes to produce antibodies against them. These antibodies are purported to cross-react with other normal cellular constituents, generating large numbers of immune complexes that are deposited throughout the body, especially in the kidneys (lupus nephritis) and the blood vessel walls (vasculitis) of all organs, including the skin. Recently it has become apparent that individuals may have a genetic predisposition to the development of some forms of the disease. Although some speculation exists that a viral agent irritates the disease, no scientific evidence has yet been found to support this theory. The apparent role of UV light in the development of lesions on exposed cutaneous surfaces is also unknown.

Systemic Lupus Erythematosus

SLE is the most common form of the disease and the form with the highest morbidity. Most of the systemic problems are related to the kidneys, where damage to the glomeruli can be severe. Patients experience widespread arthritis and arthralgia; heart and lung involvement; anemia and bone marrow depression; and diffuse vasculitis and skin rashes, most notably the “butterfly rash” over the malar areas of the face (Figure 8-39). Fatigue, malaise, fever, and psychosis are commonly found in those affected. The disease primarily affects females,

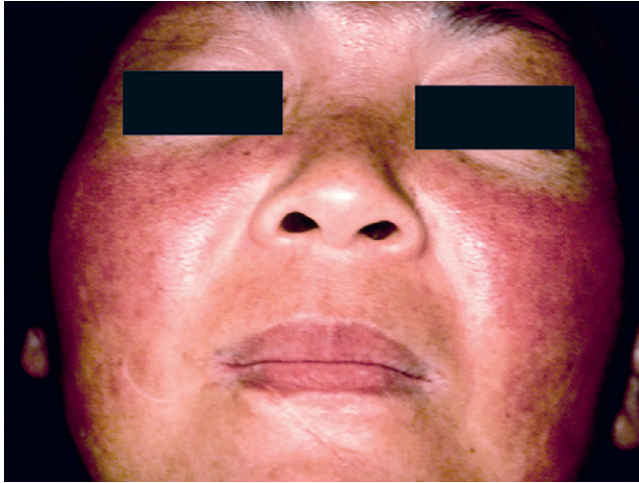


FIGURE 8-39

Lupus erythematosus. Vasculitis and skin rash over malar areas of face ("butterfly rash") that intensify with exposure to sunlight are common in most forms of the disease.

usually during the childbearing years. Oral lesions are found in 21% of patients with SLE.

Subacute Cutaneous Lupus Erythematosus

SCLE affects the skin of the upper parts of the body, with systemic and musculoskeletal components mildly involved. Chronic skin rashes are present for months but eventually heal. Symptoms of muscle and joint stiffness, malaise, and fatigue are common. Circulating ANAs and

SS-A/Ro antibodies to cytoplasmic constituents similar to those found in Sjögren's syndrome are also found.

Discoid Lupus Erythematosus

DLE is the form of the disease in which cutaneous lesions of the face, scalp, external ears, and occasionally oral mucosa are the most prominent findings. Scalp involvement with hair loss (alopecia) is also common. New skin lesions are erythematous plaques with a thick adherent scale that occludes hair follicles. Long-standing lesions are hypopigmented atrophic areas with erythematous raised borders that may be present for years.

CLINICAL FEATURES

Oral mucosal lesions occur in approximately 24% of patients affected with DLE and are similar to the oral lesions found in other forms of LE. In SLE, oral lesions are less common (present only in 21% of cases) but are often more symptomatic and involve more intra-oral structures. Oral mucosal lesions can be found in all forms of LE, appearing as annular leukoplakic areas, erythematous erosions, or chronic ulcerations (Figure 8-40). This lesion is most commonly found in patients with DLE. In milder forms an ulcer may not develop; lesions appear as an area of chronic erythema that is sensitive, often with a burning sensation. The long-standing chronic lesion may have few symptoms and be present as a leukoplakic patch that does not ulcerate. Although oral lesions are occasionally the first physical sign of LE, oral and skin lesions appear simultaneously in most cases.

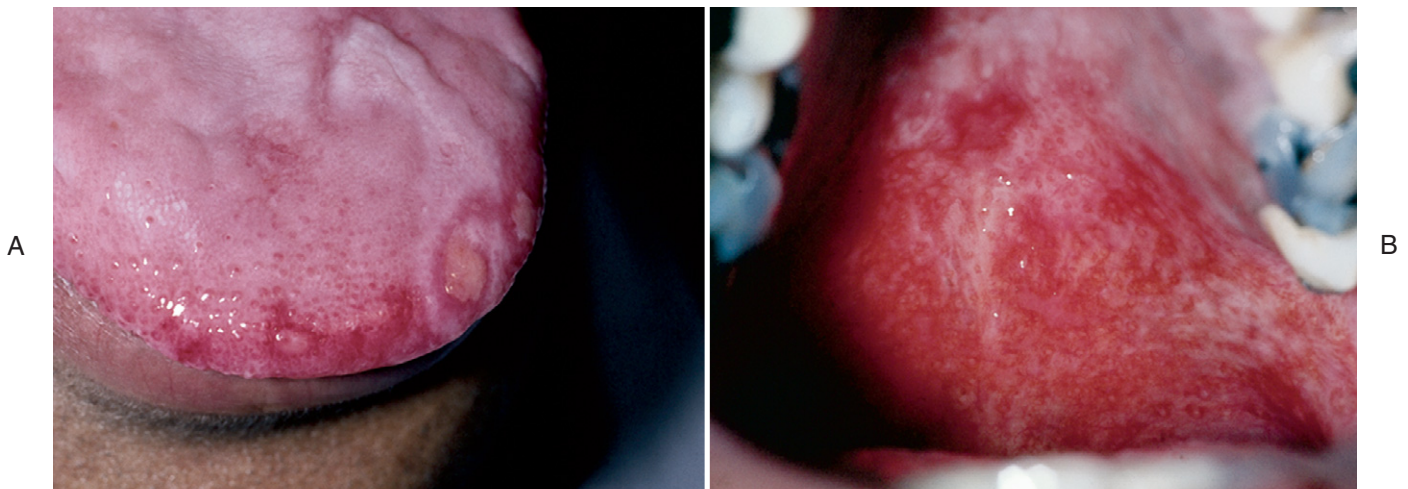


FIGURE 8-40

Lupus erythematosus. Patient with oral mucosal lesions of the tongue (**A**) and palate, consisting of diffuse and annular leukoplakic lesions, erythematous areas, and chronic ulcerations (**B**). Intraoral lesions are most frequently found in patients with the discoid form of LE but may be present to a lesser degree in all forms of the disease.

HISTOPATHOLOGY

The microscopic features of mucosal lesions of LE are remarkably similar to those found in LP and GVHD. The target antigen appears to be in the basal and parabasal layers of the epithelium, where large numbers of T lymphocytes accumulate and degeneration of cells occurs. An increase in the thickness of the basement membrane and epithelial atrophy with loss of rete peg formation is common. The presence of concentrations of lymphocytes in the immediate underlying lamina propria, deep focal accumulations of lymphocytes with germinal centers, and perivascular infiltrates of lymphocytes (Figure 8-41) is helpful in differentiating lesions of LE from those of LP. In the more chronic lesions the presence of hyperorthokeratosis and surface depressions containing keratin (keratin plugging) suggests that a lesion is LE rather than LP. Direct immunofluorescence reveals a granular linear pattern to the IgA, IgM, and IgG immunoglobulins; fibrinogen; and C3. Such a pattern is not sufficiently specific to be diagnostic for LE but can be of help in distinguishing LE lesions from LP, because LP is not usually reactive to any of the immunoglobulins. The most specific diagnostic tests for SLE are tests examining the ANAs of double-stranded DNA (dsDNA), serum rheumatoid factors, and the LE cell test. Unfortunately, these tests are usually negative in patients with DLE.

TREATMENT

Cutaneous lesions of DLE are treated with topical steroids, antimalarials, and sulfones. The more severe forms of the disease require steroids or combinations of steroids and immunosuppressive drugs such as cyclophosphamide and azathioprine. Oral lesions can be

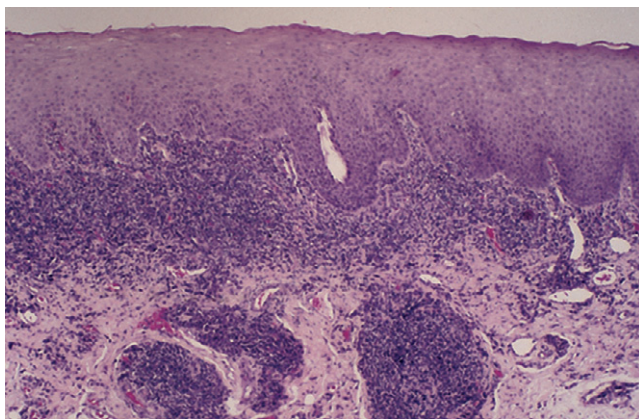


FIGURE 8-41

Lupus erythematosus. Microscopic appearance of mucosal lesions exhibiting a parakeratinizing surface with a dense infiltrate of lymphocytes in the immediate underlying connective tissue. In the deeper areas characteristic large focal and perivascular accumulations of lymphocytes are seen.

refractory to topical treatment, requiring systemic steroids to obtain relief of symptoms.

PROGRESSIVE SYSTEMIC SCLEROSIS

PROGRESSIVE SYSTEMIC SCLEROSIS

(SCLERODERMA): A generalized condition characterized by replacement of the normal connective tissue with dense collagen bundles resulting in fibrosis, loss of mobility, and altered function of organs.

Progressive systemic sclerosis (PSS) is preferred to the older term, "scleroderma." The disease has three main presentations: (1) the diffuse (classic) form, in which generalized involvement of both the body surfaces and the visceral organs is seen; (2) as part of the CREST syndrome, consisting of calcinosis (C), Raynaud disease (R), esophageal strictures (E), sclerodactyly (S), and telangiectasia (T) of the skin; and (3) the localized form, which may appear as one of three clinical subtypes referred to as *morphea*, *linear*, or "en coup de sabre." The basic disease process is a slow, continuous replacement of the usual vascular loose connective tissue with densely packed collagen bundles. This process usually results in a reduction of deep blood vessels and telangiectatic superficial vessels. When the skin becomes involved, it loses its softness and elasticity and becomes tight and firmly adhered to the underlying muscle and bone, resulting in progressive loss of mobility of the hands, joints, or other moving internal or external anatomic structures. Because of this feature, at one time the condition was referred to as "hidebound disease." The disease primarily affects females and initially appears during middle age.

The pathogenesis of the progressive fibrous replacement of the normal connective tissue is not completely known. Recent research has found circulating immune complexes that are toxic to capillary endothelial cells, which chronically damage these blood vessels and stimulate nearby fibroblasts to produce collagen. In severe diffuse forms of the disease, patients exhibit specific circulating and tissue ANAs. Some CREST syndrome patients exhibit the antibody to the protein contained within the centromere of the cell. This is most common in patients who have Raynaud disease as a prominent feature of their disease process. In some cases defective fibroblast function is the fundamental disease process.

In the diffuse form of PSS most of the skin is involved, as are the esophagus, intestines, lungs, kidneys, and heart. The skin becomes firm and immovable, with loss of adnexal structures such as hair and the sebaceous and sweat glands. A restricted oral opening and sclerodactyly are prominent in the late stages of the disease (Figure 8-42).

**FIGURE 8-42**

Progressive systemic sclerosis. Patients exhibit superficial tissue that becomes firm and immovable, resulting in contracture of the lips and a limited mouth opening (**A**) and fingers with tightly bound skin (sclerodactyly) with reduced mobility (**B**).

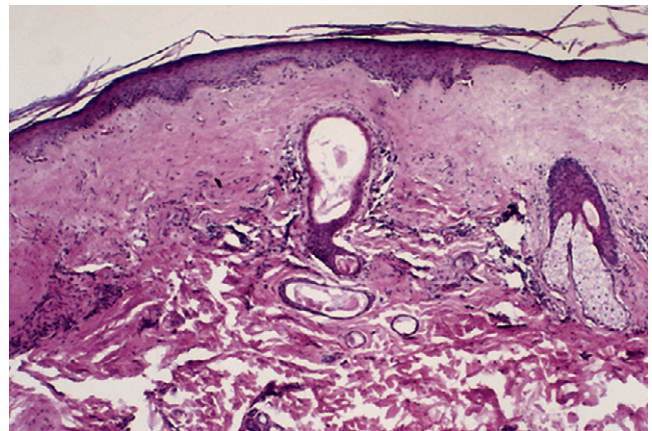
The localized form of PSS is limited to regions of the skin and does not have visceral involvement. The clinical subtypes of localized PSS merely reflect the morphologic cutaneous surfaces affected by the disease.

CLINICAL FEATURES

The oral and facial manifestations of PSS are found most often in patients with the diffuse form and those with CREST syndrome. The major oral problem is the progressive restriction of the oral opening and the loss of saliva production that leads to a xerostomia and its associated complications. These conditions, combined with dysphagia because of esophageal strictures, result in a diminished ability to eat and have the required dental care. Other findings include generalized induration of the mucosal tissue, altered tongue function, and alteration in the fibrous component of the gingiva (resulting in advanced periodontitis). Symptomatic alterations in the temporomandibular joint include clicking, crepitation, and pain is sometimes associated with erosion of bone. Cortical erosion of the bone at the angle of the mandible and the coronoid process is occasionally observed. In less than one third of the patients, widening of the periodontal membrane will be found in the late stage of the disease.

HISTOPATHOLOGY

The tissue reveals diffuse deposits of dense hyalinized collagen replacing the normal anatomic structures. In the skin the sweat glands, hair follicles, and sebaceous glands are lost, and the overlying epithelium is thinned (Figure 8-43). Hyalinization occurs around blood vessels, and adipose tissue is lost. In the early stages perivas-

**FIGURE 8-43**

Progressive systemic sclerosis. Photomicrograph of the skin reveals a dense hyalinized collagen deposit immediately below the epithelium that is replacing most dermal appendages and other anatomic structures.

cular infiltrates of mononuclear inflammatory cells are common, followed by a gradual decrease in the number of small blood vessels and a simultaneous increase in the density of the collagen.

TREATMENT

In some patients spontaneous remissions have occurred. Use of systemic steroids has been of some help in reducing the rate of progression of the disease. In general, no treatment is presently available to completely halt the disease process.

ALLERGIC REACTIONS

Allergic reactions, which occur after repeated contact with an external antigen (allergen) in previously sensitized individuals, are immune inflammatory responses mediated by the IgE immunoglobulin. After initial contact, IgE is secreted by lymphoblasts into the circulatory system where it binds to specific receptors on basophils and mast cells, sensitizing the cells to the external agent for months or years.

In 5% to 10% of the population, individuals are prone to developing large numbers of IgE-sensitized mast cells; when reexposed to the allergen, they bind it in large amounts.

Binding of the allergen to IgE antibodies attached to mast cells or basophils triggers the cells' cytoplasm to degranulate. For degranulation to occur, two surface IgE antibodies must be bridged by the same binding allergen. The released cytoplasmic granules have high concentrations of histamine, serotonin, heparin, eosinophil chemotactic factor, slow-reacting substance anaphylaxis (SRS-A), and bradykinin. The actions of these chemical mediators on the surrounding tissue account for the symptoms seen in allergic patients. The particular patient's concentration of IgE, the susceptibility of the mast cells to degranulation, the sensitivity of the endothelial and other target cells to the released mediators, and the presence of sufficient neutralizing mediators governs the severity of the patient's reactions. These factors are variable in each patient, and many are genetically determined. Thus some individuals are more prone to severe and recurring reactions than others.

CONTACT STOMATITIS

Hypersensitivity to allergens is commonly observed within the oral cavity. Because some of the most common allergens are foods, patients who are sensitive to specific foods (nuts, shellfish, cinnamon, fruits, some vegetables) will exhibit mucosal reactions soon after contact. Other allergens are chemical in nature (haptens) and require conjugation with proteins to become effective allergens. This process occurs with the aid of intraepithelial Langerhans cell, where the hapten is converted into a competent antigen and presented to the T lymphocytes for sensitization and production of IgE with specific receptors. These allergens are metals; dental materials; flavoring and other chemicals in toothpaste, mouthwash, and chewing gum; ingredients in rubber dam and latex gloves; and cosmetics such as lipstick. Drugs and other medications comprise a large category of allergens; notable are penicillin and sulfa drugs. Many of these allergens are ingested, which allows for quick access into the blood stream. In the blood stream the al-

lergens may sensitize immune cells in all parts of the body, resulting in life-threatening vasodilatation and edema of the airway and other organs. When such a reaction is severe, it is referred to as *anaphylactic shock*. Because of the large number of possible allergens, the sensitizing agent may remain undiscovered.

CLINICAL FEATURES

Erythema and edema are the usual oral mucosal reactions to the presence of a sensitizing allergen. When the gingiva is involved, the tissue is a uniform bright red in all quadrants (Figure 8-44, A). This is in contrast to the dental plaque-related gingivitis that is usually present in some locations and confined to an area close to the free gingival margin with the attached gingiva of relatively normal color. The buccal mucosa is generally puffy and dark red. Closer examination reveals that the superficial capillaries are engorged and ejected. The lips are frequently involved and appear swollen, erythematous, and subject to erosive areas and chronic ulceration (Figure 8-44, B). Patients complain of a burning sensation and sensitivity to hot,



FIGURE 8-44

Contact stomatitis. Patient with generalized erythema and edema of the gingiva (A) and swollen lips with small fissures and erosive areas caused by hypersensitivity to an unidentified allergen (B).

cold, alcohol, and spicy foods and liquids. An allergy to denture base materials is unusual, occurring only when the acrylic has been incompletely cured. In these cases, the distribution corresponds to all tissue surfaces that are in contact with the denture base. This distribution pattern distinguishes true allergic reactions to denture acrylic from the common similarly appearing acute atrophic (erythematous) candidiasis that occurs on the palate only.

HISTOPATHOLOGY

The epithelium usually exhibits intracellular and intercellular edema (spongiosis). Occasionally, vesicular formation occurs that may be located within the epithelium or at the basement membrane. The connective tissue exhibits engorged and dilated blood vessels against a background of edema and an infiltrate of lymphocytes and plasma cells. The infiltrates are often concentrated in perivascular locations, especially in the deeper areas. In some lesions the allergen elicits a heavy plasma cell response. Lesions containing dense infiltrates of plasma cells are commonly associated with allergies to flavoring in chewing gum and mouthwash and have been referred to as *plasma cell gingivitis*. Presence of an increased number of eosinophils is a frequent tissue finding in allergic reactions.

ANGIOEDEMA

ANGIOEDEMA: A recurring rapid swelling of the lips and adjacent structures in susceptible patients that occurs after contact with an allergen, antiinflammatory medication, or exposure to the elements.

Angioedema is a common clinical presentation of a group of allergic conditions with different causative pathways. The previous term, "angioneurotic edema," is no longer used, because the condition is not thought to be related to psychologic problems or other nervous system stimulation as initially described by Quincke in 1882. Within the oral area, angioedema usually develops rather quickly as a regional, painless swelling of the lips, anterior cheek, or tongue (Figure 8-45). It is of great concern when the more posterior anatomic structures are involved, because the airway becomes subject to compromise, creating an emergency situation. Upon cessation of contact with the allergen, the swelling subsides rapidly on its own, usually within 24 to 48 hours. The two basic forms of angioedema are (1) acquired and (2) hereditary.

Acquired angioedema is the most common form and is frequently the result of recent ingestion of a medication. Most of the acquired types are IgE immune mediated, particularly those initiated by peni-



FIGURE 8-45

Acquired angioedema. Patient with swelling of the lips and right cheek with transepithelial oozing and crusting of transudate that began 3 days after receiving penicillin during root canal treatment.

cillin. Other types are of a nonimmune origin, such as occurs in patients receiving nonsteroidal antiinflammatory drugs (aspirin and indomethacin). These medications act directly on the mast cell, destabilizing the cell membrane and thereby facilitating degranulation and liberating chemical mediators of inflammation. In other types, the angiotensin-converting enzyme inhibitors such as captopril and enalaprilate cause a nonimmune-mediated angioedema by enhancing the activity of bradykinin, one of the inflammatory mediators liberated from mast cells during degranulation. In some patients, exposure to cold, sun, or exercise (not ingestion of medication) is the cause of angioedema.

Hereditary angioedema, a rare form of the disease, is inherited as an autosomal dominant trait. In these patients the swelling develops after mild trauma to the area. In the oral area, lesions are frequently preceded by a tooth extraction. Unlike the acquired form, lesions of hereditary angioedema may involve the GI and respiratory tracts. Involvement of these areas usually results in a medical emergency, because intense pain and vomiting or laryngeal constriction often ensues. The hereditary form of angioedema is due to a hereditary deficiency of the C1 esterase inhibitor (C1INH) of the complement cascade. Without the inhibitor, very little provocation is required to precipitate activation of the complement system, leading to vascular dilatation and tissue edema.

POSSIBLE IMMUNE-MEDIATED REACTIONS

CHEILITIS GLANDULARIS

CHEILITIS GLANDULARIS: *Enlargement of the lower lip caused by chronic inflammation of the minor salivary glands and distention of excretory ductal structures.*

Cheilitis glandularis is an uncommon inflammatory condition of the minor salivary glands of the lower lip. Multiple causative factors have been attributed to the condition, but the basic initiating factors are still unknown. Because this condition clinically resembles cheilitis granulomatosa, a disease considered to have an immune-mediated component, it is discussed in this chapter to help differentiate the two conditions.

CLINICAL FEATURES

Cheilitis glandularis is a condition of the lower lip that occurs primarily in middle-aged and older men. The lip becomes greatly enlarged and everted, exposing the labial mucosa to the sun and atmospheric elements. The exposed surfaces become dry and pale and contain multiple small reddish nodules (Figure 8-46). The nodules represent openings of excretory ducts of minor salivary glands that have become congested with retained mucin. With bimanual palpation, mucin can be expressed from the nodules. This is a useful diagnostic test for this condition.

HISTOPATHOLOGY

The connective tissue of the lower lip contains multiple chronically inflamed minor salivary glands with distended and tortuous excretory ducts. The ducts generally contain inspissated mucin with fibrous tissue, lymphocytes, and plasma cells replacing the acini. The normal ductal lining exhibits focal areas of metaplasia to a stratified squamous epithelium. Bacteria commonly enter the ductal structures, causing the production of purulent



FIGURE 8-46

Cheilitis glandularis. A long-standing enlarged lower lip with a pale, dry surface containing multiple small raised papules (enlarged duct openings) is characteristic of this condition.

exudate, which replaces the mucin. In this acute form of the disease, many patients experience associated deep abscesses throughout the lip, with frequent draining sinus tracts.

TREATMENT

Surgery is the preferred method of treatment, usually in the form of a vermilionectomy. In more severe and long-standing conditions, extensive surgical reduction of the lip may be required. Untreated affected lips are thought to have an increased risk of developing carcinoma.

OROFACIAL GRANULOMATOSIS

OROFACIAL GRANULOMATOSIS: *A clinicopathologic term describing a group of oral conditions of varying causes, all with a similar microscopic feature of noncaseating granulomas.*

The spectrum of orofacial granulomatosis includes patients with oral manifestations of Crohn disease, the localized oral entity of cheilitis granulomatosa, and a collection of pathophysiologic findings called *Melkersson-Rosenthal syndrome (MRS)*. In some cases, patients with orofacial granulomatosis will develop the typical bowel symptoms of Crohn disease in the ensuing months to years. Others will eventually be found to have sarcoidosis, a reaction to an infection or foreign material or a hereditary predisposition for granulomas such as chronic granulomatous disease (CGD) of childhood. The use of the umbrella term of *orofacial granulomatosis* is valuable, because it immediately places the initial findings in a category and indicates the need to search for the specific underlying or local cause of the condition.

Oral Crohn Disease

Crohn disease is a chronic inflammatory disease of the GI tract occurring in any location from the mouth to the anus. In 90% of cases, the terminal ileum is involved alone or in combination with the ascending colon. When located in the large and small bowel area, it consists of small abscess and noncaseating granulomas that may, with time, extend throughout the bowel wall and even into the serosa. The disease characteristically has large skip areas of normal tissue between areas of abscesses, granulomas, fibrosis, and fistulas.

CLINICAL FEATURES

The condition rarely occurs in the oral cavity and adjacent upper GI tract; when it does, it is varied in nature, depending upon the specific oral structure involved. The most frequently affected area is the buccal mucosa, where it often exhibits a cobblestone pattern. In the vestibule, lesions are commonly linear hyperplastic folds with ul-

cers. When the lips are involved they are diffusely swollen and indurated, closely resembling cheilitis granulomatosa or MRS. Lesions of the gingiva and alveolar mucosa are less frequent but when present appear as a granular and erythematous swelling. Although multiple aphthous-like ulcers can appear in any location, they are the predominant presentation on the palate. In many cases, more than one intraoral site will become involved during the course of the disease. The oral lesions may become present months to years before abdominal symptoms occur or the diagnosis of Crohn disease is made.

HISTOPATHOLOGY

Lesions may be either sarcoidlike, noncaseating granulomas or nonspecific aphthouslike ulcerations. The granulomas are composed of a central accumulation multinucleated giant cells with peripherally aligned nuclei and epithelioid cells. This central area is surrounded by lymphocytes and fibrous tissue. The ulcers may be small and multiple or large and deep. Combinations of both tissue types may be found.

TREATMENT

Patients are managed systemically with a combination of antibacterial and antiinflammatory medications. Commonly used medications are sulfasalazine and other 5-ASA agents, azathioprine, and ciprofloxacin.

Cheilitis Granulomatosa

CHEILITIS GRANULOMATOSA: A recurrent or persistent enlargement of the lip commonly associated with Melkersson-Rosenthal syndrome and consisting of noncaseating granulomas, generalized edema, and vascular changes.

Cheilitis granulomatosa is a recurrent or persistent enlargement of the lip that is commonly associated with Melkersson-Rosenthal syndrome (MRS). The other features of MRS are a generalized orofacial swelling, peripheral facial nerve paralysis, and a fissured tongue. The cause of the condition is unknown.

CLINICAL FEATURES

Affected patients are found in all age groups, with a median age of 25 years. Exacerbation of the generally enlarged lower lip occurs on a regular basis and may be associated with other intraoral swellings, particularly of the palate and the floor of the mouth. In addition to the cosmetic problem, the enlarged and disfigured lip provides difficulties for the patient when eating, drinking, and speaking (Figure 8-47).

HISTOPATHOLOGY

The characteristic feature of the tissue is the presence of multiple noncaseating granulomas that are located close to the vascular structures. The granulomas are composed of epithelioid cells and giant cells (Figure 8-48); nearby aggregates of lymphocytes and plasma cells are occasionally seen. Generalized edema and dilated blood vessels are also present throughout the connective tissue.

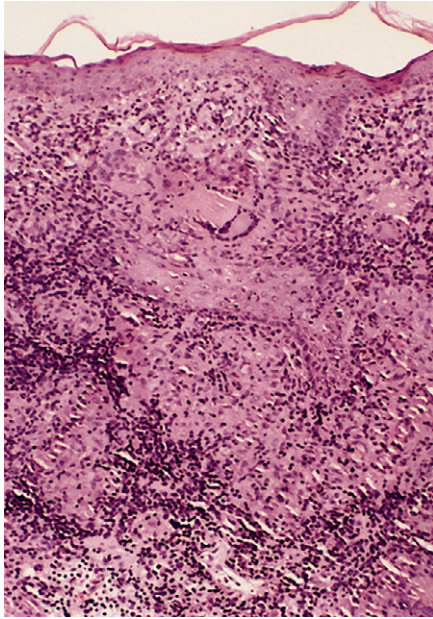
TREATMENT

The most successful treatment has been the identification and removal of coexisting infections, often of odontogenic origin. Surgical resection of the enlarged and usually everted lip is sometimes effective. Intralesional injection of steroid solutions has generally shown little effect.



FIGURE 8-47

Cheilitis granulomatosa. Enlarged and disfigured lower lip, which is apparent in frontal (**A**) and lateral (**B**) views. The condition also produces difficulties in eating and speaking.

**FIGURE 8-48**

Cheilitis granulomatosa. Microscopic features reveal multiple focal granulomas composed of epithelioid cells and giant cells surrounded by lymphocytes, plasma cells, and edematous connective tissue.

Melkersson-Rosenthal Syndrome

Melkersson-Rosenthal syndrome (MRS) is a rare disorder of unknown cause, characterized by a triad of recurrent orofacial swelling, intermittent facial paralysis, and fissured (plicated) tongue. Exacerbations and recurrences are common. Fissured, reddish-brown, swollen lips and edema of the face characterize the orofacial swelling. The facial palsy is indistinguishable from Bell palsy. The fissured tongue is seen in one third to one half of patients. Although the tongue condition is the least common manifestation, its presence is of immense value in establishing a diagnosis.

Unfortunately the classic triad is infrequently observed, making this diagnosis difficult. Most commonly the condition has only one or two of the classic features. When only the lip swelling is present, the diagnosis of cheilitis granulomatosa is usually made rather than MRS. The histologic findings of noncaseating, sarcoidlike granulomas is supportive of the diagnosis. These granulomas are not invariably present, and their absence does not exclude the diagnosis of MRS if other features are present.

CHRONIC GRANULOMATOUS DISEASE

Chronic granulomatous disease (CGD) is not a specific oral condition but can sometimes have oral lesions that resemble the granulomas of the group of lesions usually

referred to as *orofacial granulomatosis*. Because most patients are diagnosed in early childhood, it is sometimes referred to as *CGD of childhood*. It is reported to have an incidence of 1:200,000, making it a somewhat uncommon occurrence. CGD is a heterogeneous disorder characterized by chronic and recurrent infection caused by a lack of superoxide and its derivatives in the blood neutrophils, monocytes, and eosinophils. Superoxide is required for a metabolic respiratory burst to effectively kill catalase-positive bacteria. The disease is a hereditary immunodeficiency transmitted in two genetic forms: (1) X-linked and (2) autosomal recessive. In the X-linked form, a coding for a protein required on the plasma membrane of the phagocytic cells is not expressed. The protein appears to be a constituent of cytochrome b, a component of leukocyte oxidase, which catalyzes the cell respiratory burst. A gene coded for the co-factors necessary for oxidase expression controls the autosomal recessive form.

Patients with CGD suffer from recurrent bacterial and fungal infections in the form of pneumonia, abscesses, and lymphadenitis; however, some patients remain undiagnosed until adulthood. Effective therapy for CGD is not available. Long-term use of antibiotics may be helpful.

SARCOIDOSIS

SARCOIDOSIS: A chronic disease affecting the skin, mucosa, salivary glands, lungs, and other organs; consists of multiple noncaseating epithelioid granulomas and fibrosis of adjacent tissue.

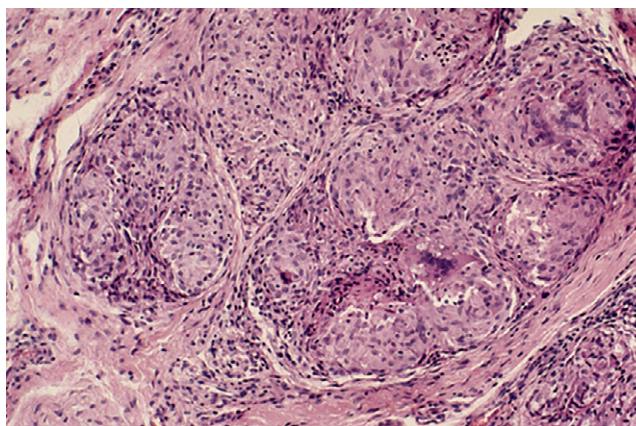
Sarcoidosis is a chronic disease consisting of multiple granulomas of the skin, mucosal surfaces, salivary glands, lungs, and occasionally other major organs. At present, the cause of sarcoidosis is unknown. Research has revealed some features of the disease that may eventually be useful in identifying the causative factors: (1) some ethnic groups are more susceptible than others; the hormonal status of the patients may play a role; (2) the patients' major histocompatibility antigen status is important, particularly those having HLA-B5, -B7, -B8, HLA-A9, HLA-Cw7, and HLA-DR3 types; (3) patients are allergic to antigens found in some infectious agents such as mumps, tuberculosis, and *Candida*; (4) often patients have reduced levels of circulating T lymphocytes; (5) some patients have altered CD4/CD8 ratios; and (6) some have elevated levels of serum lysozymes and serum angiotensin-converting enzymes.

CLINICAL FEATURES

Sarcoidosis is common in black populations of the Caribbean, Puerto Rico, and Africa. African Americans have a higher incidence of the disease than the rest of

**FIGURE 8-49**

Sarcoidosis. The soft palate contains a firm raised diffuse nodular lesion with a focal area of ulceration.

**FIGURE 8-50**

Sarcoidosis. Tissue exhibits multiple noncaseating granulomas consisting of epithelioid cells and multinucleated giant cells and surrounded by thin bands of fibrous tissue. Few lymphocytes are observed in the adjacent connective tissue.

the population. In America, the disease is usually contracted before the age of 40 and is significantly more frequent in women than men. In Europe the disease is found in a slightly older age group and is equally distributed among the sexes.

The patients' symptoms are generally nonspecific. Patients complain of a general lack of energy and difficulty in breathing. The lungs appear to be initially involved with extension through the lymphatics to the hilar and mediastinal lymph nodes. Many patients have multiple erythematous skin nodules, swelling of the parotids or submandibular glands, or both. Other involvement of the head and neck area is common, with lymph nodes exhibiting enlargement and lesions present in and around the nasal passages. Lesions have been known to develop in bone but are rare. Approximately 25% of patients will have eye involvement, particularly of the uveal tract. A combination of lesions of the uveal tract, parotid gland, and seventh cranial nerve has been described as Heerfordt syndrome (uveoparotid fever).

Oral lesions appear as diffuse submucosal enlargements or focal firm nodules. Ulceration is uncommon, and lesions are usually completely symptomless. Lesions have been reported on the lips, tongue, buccal mucosa, gingiva, hard and soft palate (Figure 8-49), and floor of the mouth.

HISTOPATHOLOGY

The tissue contains multiple granulomas in a nodular pattern, each consisting of an accumulation of epithelioid macrophages and multinucleated giant cells (Figure 8-50). The granulomas are similar to those found

in tuberculosis; however, the central caseating necrosis is absent and lymphocyte infiltrate is reduced. The periphery of each granuloma is composed of a cellular fibrous connective tissue. The multiple nuclei of the giant cells are often arranged in a ring around the periphery and may additionally contain some stellate-shaped structures that have been described as *asteroid bodies*. Electron microscopy reveals that these structures are phagocytized cellular debris. Because the cellular features are similar to other infectious or foreign-body granulomas, bacterial and fungal stains are usually applied and the tissue is viewed with polarized light to rule out these causative factors.

DIAGNOSIS

In disseminated cases, urinalysis will reveal an increase in calcium levels and serum analysis will reveal an increase in calcium, immunoglobulins, lysozymes, and angiotensin-converting enzymes. The traditional Kveim test is performed by injecting a suspension of human antigenic extract from the spleen tissue of patients with sarcoidosis into the forearm of patients suspected of having the disease. Positive patients will develop a sarcoid lesion in 4 to 6 weeks.

TREATMENT

Patients are generally treated with steroids, usually prednisone, if lung lesions are present. Immunosuppressant drugs have also been used either alone or in combination with other modalities but are generally thought to be ineffective. Spontaneous resolution of lesions is also known to occur. Prognosis is good in nearly all treated cases.

PYOSTOMATITIS VEGETANS

Pyostomatitis vegetans is an inflammatory disorder of the mucous membranes and occasionally of skin. It is characterized by the presence of multiple pustular lesions that rupture and result in widespread focal ulcerations. On the skin, a similar condition is referred to as *pyodermatitis vegetans*. Its presence is notable as an indicator of inflammatory bowel disease, usually ulcerative colitis. It has also been associated with the more chronic and granulomatous Crohn disease of bowel.

CLINICAL FEATURES

Pyostomatitis vegetans has a distinct male-to-female preponderance of 3:1 and can affect all age groups. The oral mucosa may have a variety of appearances. Most commonly it appears as large erythematous granular patches containing pustules and superficial ulcerations. Although any part of the mouth can be involved, the buccal and labial attached gingiva, buccal mucosa, and hard and soft palate most commonly contain lesions. The tongue and floor of the mouth are usually spared. The appearance and distribution of lesions will vary over time. Symptoms are usually mild, with occasional bouts of mild fever and lymphadenopathy. The presence of an elevated peripheral blood eosinophilia is a feature of ulcerative colitis and a valuable aid in establishing the diagnosis when it appears that only oral lesions are present.

HISTOPATHOLOGY

The tissues are composed of characteristic microabscesses with large numbers of eosinophils in both the overlying epithelium and the immediate underlying connective tissue. In the deeper tissues, a mixed inflammatory cell infiltrate is present with a prominent eosinophil population. The inflammatory cell infiltrate may be concentrated in perivascular locations.

TREATMENT

Although oral lesions of pyostomatitis vegetans may be present without the patient having a diagnosis of ulcerative colitis, the disease is usually present to some degree. In general, the course and severity of the oral lesions reflect that of the colon; therefore the successful management of the oral lesions is tied to the effective management of the GI disease. Topical steroids have been used with some success for oral lesions. GI disturbances are usually managed with a variety of approaches. These include diet management, correction of deficiencies because of malabsorption, psychotherapy, antibiotics, systemic steroids, and other immunosuppressive therapy. In severe recalcitrant cases, partial or total colectomy has resulted in immediate remission of oral lesions.

WEGENER GRANULOMATOSIS

Wegener granulomatosis (WG) is an uncommon disease consisting of an inflammatory granulomatous process characterized by severe vasculitis and necrosis involving mainly the upper and lower respiratory system and kidneys. Systemically, patients may exhibit symptoms of widespread vasculitis such as hemoptysis, chest pain, skin ulcers, multiple arthritis, and high levels of antineutrophil cytoplasmic antibody (cANCA). The head and neck area is involved in 90% of cases, and oral lesions are rare (2% to 5% of cases). The majority of the head and neck lesions are located in the nasosinus area, with rhinorrhea, sinusitis, otitis media, and destruction of the nasal septum common signs and symptoms.

CLINICAL FEATURES

The oral lesions are most commonly described as a granulomatous hyperplastic gingivitis that appears to originate in the interdental papilla. Such lesions are deep red, nodular, and friable and have been referred to as “strawberry gingivitis,” because of their resemblance to overripe strawberries. Other oral lesions may be ulcers and perforations of the palate and swelling and desquamation of the lips.

HISTOPATHOLOGY

In the large lesions of the upper airway, the tissues feature a prominent vasculitis with zones of necrosis and fibrinoid deposits in a general background of granulomas. Eosinophils and multinucleated giant cells are commonly encountered. The gingival lesions seldom exhibit the vasculitis and focal areas of fibrinoid necrosis; instead they appear as nonspecific granulomatous reactions, making a tissue diagnosis difficult.

TREATMENT

WG used to be uniformly fatal once the kidney was affected. Although steroids give some symptomatic relief, the most effective treatment is obtained by combining them with cyclophosphamide. With the combined medication, complete remission is achieved in 75% of patients and marked improvement in 90%. Patients who advance to irreversible kidney disease will require transplants.

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CHAPTER OUTLINE

FIBROUS TISSUE

- Hyperplasias
 - Focal Fibrous Hyperplasia (Irritation Fibroma)
 - Peripheral Ossifying Fibroma
 - Peripheral Giant Cell Granuloma
 - Inflammatory Fibrous Hyperplasia
 - Inflammatory Papillary Hyperplasia
 - Hyperplastic Gingivitis
 - Hereditary Gingival Fibromatosis
 - Drug-Induced Gingival Hyperplasia
- Benign Fibrous Neoplasms
 - Fibromatosis, Myofibromatosis, Myofibroma, and Desmoplastic Fibroma
 - Nodular Fasciitis
 - Benign Fibrous Histiocytoma
 - Benign Solitary Fibrous Tumor
- Malignant Fibrous Neoplasms
 - Fibrosarcoma, Malignant Fibrous Histiocytoma, and Malignant Solitary Fibrous Tumor

NEURAL TISSUE

- Hyperplasia
 - Traumatic Neuroma
 - Palisaded Encapsulated Neuroma
- Hamartomas
 - Multiple Endocrine Neoplasia Syndrome
- Benign Neoplasms
 - Neurilemoma
 - Neurofibroma
 - Granular Cell Tumor
 - Congenital Gingival Granular Cell Tumor
 - Neuroectodermal Tumor of Infancy
- Malignant Neoplasm
 - Neurogenic Sarcoma

MUSCLE TISSUE

- Neoplasms
 - Leiomyoma
 - Rhabdomyosarcoma

ADIPOSE TISSUE

- Neoplasms
 - Lipoma
 - Liposarcoma

VASCULAR TISSUE

- Hyperplasia
 - Pyogenic Granuloma
- Hamartomas and Neoplasms
 - Hemangioma
 - Lymphangioma
 - Angiosarcoma
 - Kaposi Sarcoma

OSSEOUS AND CARTILAGINOUS TISSUE

- Developmental Lesions
 - Soft Tissue Osteoma
 - Osseous and Cartilaginous Choristoma
- Reactive Lesion
 - Myositis Ossificans



ADDITIONAL KEY TERMS

Alveolar rhabdomyosarcoma
 Arteriovenous malformations
 Benign neoplasms
 Central neurofibroma
 Choristoma
 Cystic hygroma
 Desmoplastic fibroma
 Ectomesenchymal chondromyxoid tumor
 Embryonal rhabdomyosarcoma
 Encephalotrigeminal angiomatosis
 Epulis
 Epulis fissuratum
 Fibromatoses
 Gardner syndrome
 Giant cell fibroma
 Hemangioendothelioma
 Hemangiopericytoma
 Herniated buccal fat pad
 Irritation fibroma
 Multiple lipoblastomatosis
 Multiple neurofibromatosis
 Myofibroma
 Myofibromatosis
 Myxoid neurofibromas
 Nerve sheath myxoma
 Neurothekeoma
 Peripheral fibroma
 Pleomorphic lipoma
 Pleomorphic rhabdomyosarcoma
 Plexiform neurofibroma
 Port-wine stain
 Pregnancy gingivitis
 Pregnancy tumors
 Pseudopockets
 Puberty gingivitis
 Rhabdomyoma
 Sarcomas
 Torticollis
 Varix
 Vascular leiomyoma
 von Recklinghausen disease

The term *tumor*, which literally means *a swelling*, frequently causes confusion because it is used by some clinicians to refer to true neoplasms and by others to indicate the presence of any common overgrowth of tissue because of chronic injury. Within the oral cavity most of the so-called tumors are not true neoplasms but are hyperplastic reactions of connective tissue to chronic injury or irritation. The hyperplastic lesions are referred to as *reactive proliferations*, because they represent self-limiting growths of fibroblastic tissue or a mix-

ture of fibrous and vascular tissue resulting from chronic irritations such as cheek biting, ill-fitting dental appliances, or the negative pressure exerted by dentures. Within the oral cavity most local irritants are physical and stimulate the submucosal connective tissue, periodontal ligament, or the periosteum. The latter two locations become involved when the irritant is localized to the alveolus or gingival sulcus.

The true **benign neoplasms** of connective tissue found within the oral cavity arise from fibroblasts, endothelia, skeletal muscle, smooth muscle, lipocytes, nerve sheaths, and osteoprogenitor cells. Most are slow growing, but some are aggressive, causing extensive local destruction. Malignant connective tissue tumors, termed *sarcomas*, are rare. Their detection while still in the early stages of development is extremely important in providing the best opportunity for cure. In addition to local

BOX 9-1**Connective Tissue Neoplasms****BENIGN**

Desmoplastic fibroma
 Benign fibrous histiocytoma
 Neurilemoma/neurofibroma
 Granular cell tumor
 Leiomyoma
 Rhabdomyoma
 Lipoma
 Hemangioma
 Lymphangioma

MALIGNANT

Fibrosarcoma
 Malignant fibrous histiocytoma
 Neurogenic sarcoma
 Malignant granular cell tumor
 Leiomyosarcoma
 Rhabdomyosarcoma
 Liposarcoma
 Angiosarcoma/Kaposi sarcoma
 Lymphangiosarcoma

BOX 9-2**Oral Connective Tissue Lesions by Age Groups****INFANTS**

Congenital gingival granular cell tumor
 Pigmented neuroectodermal tumor of infancy

ADULTS

Reactive hyperplasia
 Neural tumors
 Granular cell tumor
 Lipoma
 Sarcoma

CHILDREN

Reactive hyperplasia
 Fibromatosis
 Neuroma
 Hemangioma
 Lymphangioma
 Sarcoma

aggressiveness, all sarcomas have the potential for metastasis. The degree of malignancy varies, and some are more life threatening than others. Unlike carcinomas that spread through the lymphatics, most sarcomas tend to spread via hematogenous routes, making dissemination more rapid and widespread. Box 9-1 lists benign and malignant connective tissue neoplasms found in the oral, head, and neck regions. Lesions of the oral connective tissue tend to be more common in some age groups and uncommon or even nonexistent in others (Box 9-2).

FIBROUS TISSUE

Fibrous proliferations occur as a result of reaction to injury, spontaneous benign neoplastic transformation, and malignant transformation of fibroblastic cells. The reactive hyperplasias are by far the most common growths encountered in the oral regions. True benign fibroblastic neoplasms or fibromas probably do not occur within the oral submucosa. The benign focal soft tissue growths found within the oral cavity are the result of reactive hyperplasias and are composed primarily of one or more of the following connective tissue components: mature collagen, focal bone formation, endothelial cells, and multinucleated giant cells.

When a reactive focal connective tissue proliferation is confined to the gingiva and its exact histologic nature is unknown, it is clinically designated as an **epulis**. The most common lesions referred to as *epulides* are **peripheral fibroma**, peripheral ossifying fibroma, pyogenic granuloma, and peripheral giant cell granuloma (Box 9-3 and Figure 9-1).

Although the fibromatoses and fibrous histiocytomas are aggressive fibroblastic proliferations, they are considered by some sources to be reactive in nature instead of neoplastic. This is in spite of the fact that a history of injury to the area is seldom found. In this chapter, fibromatosis, myofibromatosis, nodular fasciitis,

BOX 9-3

Common Reactive Hyperplasia of Gingival Connective Tissue (Epulis)

Peripheral fibroma
Peripheral ossifying fibroma
Pyogenic granuloma (pregnancy tumor)
Peripheral giant cell granuloma

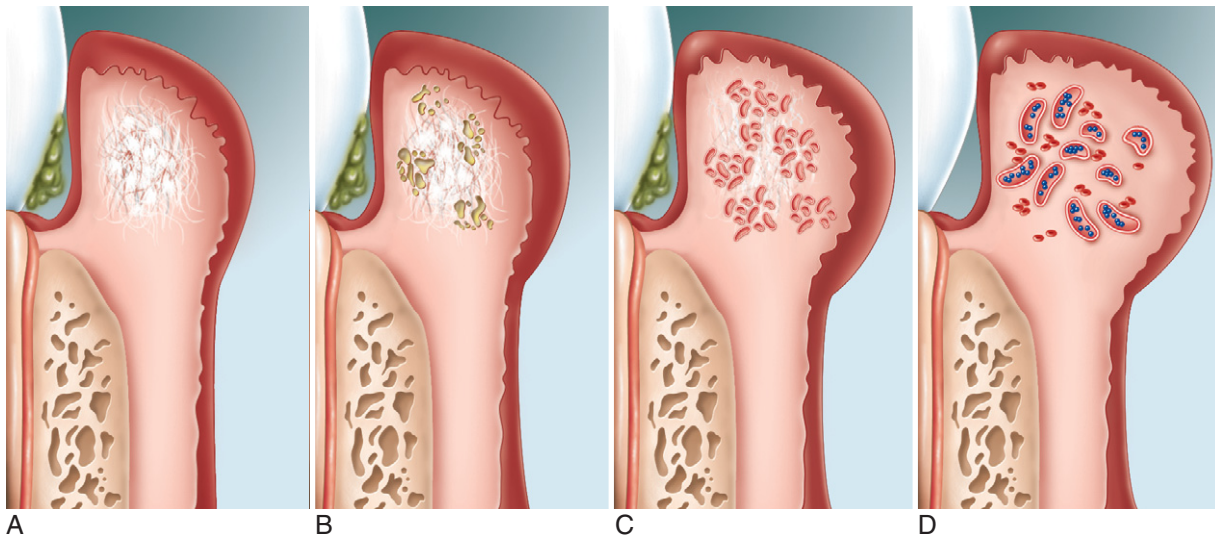


FIGURE 9-1

Distinguishing histologic features of common reactive hyperplasia of gingival connective tissue collectively designated as an epulis. Most lesions are thought to be reactive to a chronic irritant (represented here as subgingival calculus). **A**, Peripheral fibroma: hyperplasia of suprapariosteal tissues resulting in overproduction of dense collagen (white double lines). **B**, Peripheral ossifying fibroma: hyperplasia of periodontal membrane resulting in a cellular lesion consisting of fibroblasts and collagen (white) and cemental and bone deposits (yellow-green). **C**, Pyogenic granuloma: hyperplasia of a vascular component of gingival connective tissue resulting in a cellular lesion composed of endothelial cells and small capillaries (light red). **D**, Peripheral giant cell granuloma: hyperplasia of the periosteum resulting in the overproduction of a vascular component and mononuclear and multinucleated giant cells resembling osteoclasts (pink structure with blue dots).

and benign fibrous histiocytoma are classified as *benign neoplasms*. The malignant tumor derived from the fibroblast, is fibrosarcoma, an uncommon neoplasm encountered primarily in children and young adults. Most of the fibroblastic lesions arise within the soft tissue, but on occasion lesions are encountered within bone, the mandible being affected more often than the maxilla.

HYPERPLASIAS

Focal Fibrous Hyperplasia (Irritation Fibroma)

FOCAL FIBROUS HYPERPLASIA: *Hyperplasia of fibrous connective tissue that evolves in response to chronic irritation in which extensive elaboration of collagen resembling scar tissue exists.*

A focal fibrous hyperplasia is not a true neoplasm of fibroblasts but an exuberant reaction to chronic injury in which the production of mature bundles of collagen predominates. Cheek and lip biting, in addition to denture irritation, are the most common contributing factors. The resulting lesion, commonly referred to as *irritation fibroma*, represents a pathologic overgrowth of both fibroblasts and their collagenous products. It is the most common nodular swelling found within the oral cavity.

CLINICAL FEATURES

Focal fibrous hyperplasia is most often encountered in adults and is primarily located on the gingiva (Figure 9-2), lips, and buccal mucosa (Figure 9-3). Other common sites are the borders of the tongue. These nodular lesions usually occur on the soft tissue in the plane of the occlusal line. The clinical appearance of irritation fibroma is that of a domelike growth with a smooth mucosal surface of normal coloration. Ulceration is rare yet

may occur if the patient continues to irritate the swelling. Surface hyperkeratosis is sometimes encountered and is probably the result of a low-grade chronic irritation of the overlying epithelium. Lesions may remain the same size for many years.

It is of importance that they cannot be positively diagnosed by clinical examination only because other mesenchymal tumors may show similar clinical features. When the irritant is removed, lesions often become slightly smaller as the inflammatory component diminishes, yet they will not completely regress. For this reason it is usually recommended that they be excised and submitted for microscopic examination. When focal fibrous hyperplasia is on the attached gingiva in the area of the gingival sulcus or interdental papilla, it is sometimes termed *peripheral fibroma*. The term *peripheral* is used to distinguish this innocuous lesion from the more aggressive fibrous lesion that may occur centrally within the jaws. It is surmised that the gingival reactive proliferations evolve from an irritant that becomes entrapped within the gingival sulcus. Toothpick fragments, food debris, and calculus are common causative factors. Unfortunately, often at the time of clinical examination, no exogenous irritant is found within the sulcus. By the time the lesion has evolved, the irritant has probably dissolved or has been extruded.

HISTOPATHOLOGY

The surface epithelium may be intact, exhibit hyperorthokeratosis, or show foci of ulceration. This epithelium overlies an underlying mass of dense, fibrous connective tissue composed of significant amounts of mature collagen in a scarlike pattern (Figure 9-4). The spindle-shaped fibroblasts, common in some of the indeterminate fibrous lesions, are sparse. The fibroblastic nuclei are monomorphic in character, and the overall appearance is one of hypocellularity.



FIGURE 9-2
Focal fibrous hyperplasia. When located on the attached gingiva, lesions are referred to as peripheral fibroma.



FIGURE 9-3
Focal fibrous hyperplasia. In nongingival locations, lesions are commonly referred to as irritation fibroma.

A histologic variant of focal fibrous hyperplasia, referred to as *giant cell fibroma*, occurs in the oral mucosa and has a counterpart that is occasionally encountered on the skin and genitalia. The giant cell fibroma is also considered to be a reactive fibrous proliferation. The name given to this variant is based on the presence of binucleated and trinucleated fibroblasts that tend to occur in close proximity to the overlying epithelium. These binucleated and trinucleated cells have oval, monomorphic-appearing nuclei with copious eosinophilic cytoplasm. They often assume a stellate appearance, resembling a manta ray. When ulceration occurs, a mononuclear inflammatory cell infiltration occurs. The peripheral fibroma of the gingiva will usually show histologic features identical to the irritation fibroma located in other oral locations. A hypocellular fibrous reaction is encountered with mature collagen fibers.

TREATMENT

Local excision is the treatment of choice, and the lesions seldom recur. They will not involute spontaneously, because the excess collagen found is permanent. The giant cell fibroma variant appears to be no different in behavior from the focal fibrous hyperplasia. The peripheral fibroma of the gingiva is also treated by local excision but must be accompanied by periodontal root planing to ensure that all sources of irritation are eliminated.

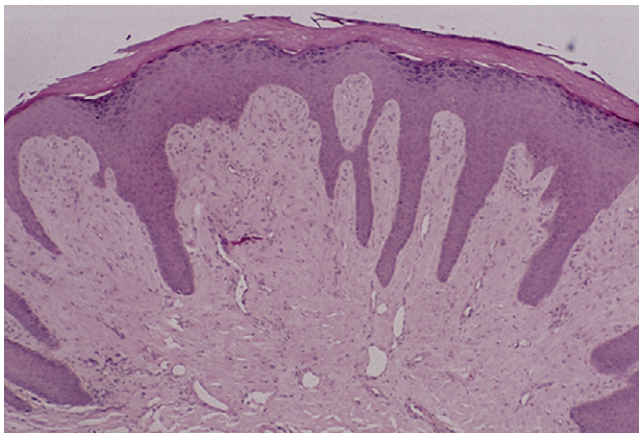


FIGURE 9-4

Focal fibrous hyperplasia. Microscopic appearance consisting of dense bundles of collagen. Because the lesion is usually chronically irritated, hyperorthokeratosis is commonly found on the surface of the epithelium.

Peripheral Ossifying Fibroma

PERIPHERAL OSSIFYING FIBROMA A gingival nodule consisting of a reactive hyperplasia of connective tissue containing focal areas of bone.

The peripheral ossifying fibroma is a reactive fibrous proliferation, probably of periosteal or periodontal ligament origin. Because the periosteum and periodontal ligament contain cells that synthesize both bone and cementum, the proliferation includes cells with osteogenic potential. These lesions are related to other reactive gingival swellings, because irritation is considered to play a significant role in the cause.

CLINICAL FEATURES

This reactive lesion is more common in women and tends to occur during the reproductive years, especially the third and fourth decades. It is usually not found in children and the elderly. Peripheral ossifying fibroma is an epulis that emanates from the interdental papillae, although occasionally it is seen to arise from the facial or lingual attached gingiva (Figure 9-5). Invariably, the mass originates from within the periodontal ligament, where an irritant is thought to be responsible for stimulating periodontal ligament fibroblasts that also possess osteogenic and cementogenic potential. The overlying mucosa may be smooth and of normal coloration, or there may be foci of surface ulceration. They are hard to palpate and are fixed to the underlying tissue. Dental radiographs will often disclose radiopacities within the soft tissue swelling.

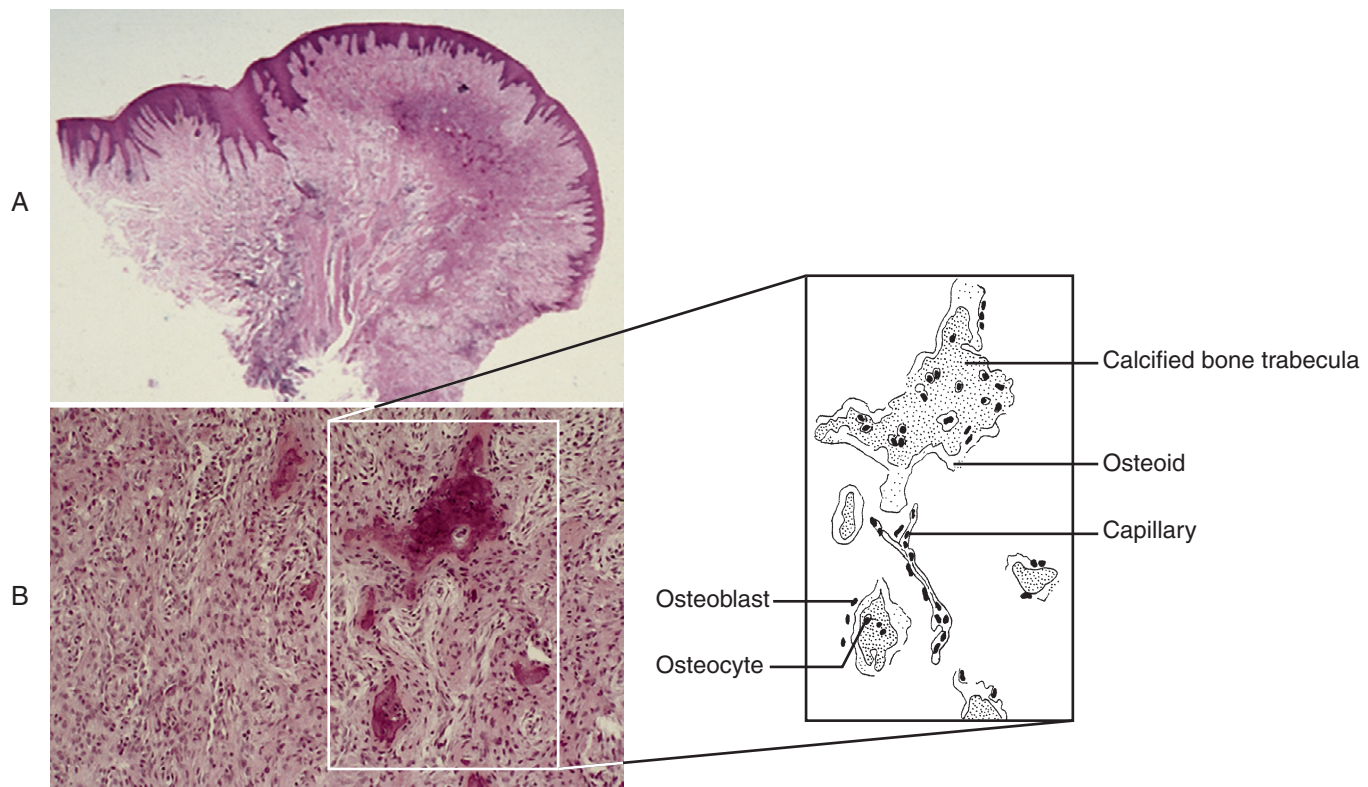
HISTOPATHOLOGY

Within the connective tissue are diffuse sheets of fibroblasts with plump monomorphic nuclei. The overall picture is one of hypercellularity, with the collagenous component somewhat hyalinized. No true capsule exists; the hypercellular zones slowly merge with mature fibrous and granulation tissues around the periphery (Figure 9-6, A). In focal areas, osteoid deposits can be identified; although some may contain lacunae with



FIGURE 9-5

Peripheral ossifying fibroma. Lesions frequently become large and interfere with mastication.

**FIGURE 9-6**

Peripheral ossifying fibroma. **A**, Low-power microscopy reveals a rounded mass with a zone of cellular connective tissue (*right side of lesion*). **B**, High-power microscopy of cellular zone and accompanying tracing demonstrates the islands of calcified bone trabeculae, osteoid deposits, osteoblasts, and osteocytes that distinguish the lesion from a peripheral fibroma.

osteocyte nuclei, others are acellular (Figure 9-6, *B*). Rarely, thick mature trabeculae of bone are seen. The hypercellular component usually extends into the periodontal ligament.

TREATMENT

Peripheral ossifying fibroma must be excised to include the periodontal ligament. Thorough periodontal root planing is recommended to remove irritants trapped within the sulcus.

Peripheral Giant Cell Granuloma

PERIPHERAL GIANT CELL GRANULOMA: *An extraosseous nodule composed of a proliferation of mononuclear and multinucleated giant cells with an associated prominent vascularity found on the gingiva or alveolar ridge.*

The peripheral giant cell granuloma is a hyperplastic reaction of the gingival connective tissue in which the histiocytic and endothelial cellular components pre-

dominate. These two cell types are intermingled and arranged in a lobular pattern separated by a fibrous connective tissue containing large sinusoidal blood vessels. The name of the lesion is derived from the tendency of the mononuclear histiocytes to form large multinucleated giant cells; the peripheral (extraosseous) location of the lesion in contrast to the larger, more aggressive central (intraosseous) giant cell lesions; and their clinical course of the gingival lesions, which is similar to a reactive granulomatous response. The factors that initiate the lesions are unknown. Lesions containing similar giant cell tissue are found in other parts of the body but are mainly within bone. These central bony lesions may be associated with hyperparathyroidism (brown tumor), other benign fibroosseous lesions, a hereditary condition (cherubism), or they may exist as a neoplasm (giant cell tumor).

CLINICAL FEATURES

Peripheral giant cell granuloma is found in all age groups, with a slight peak in incidence in adults around 30 years of age and in children during the

mixed dentition stage. It is more common in females and is nearly equally distributed between the mandible and maxilla. Although it occurs in both anterior and posterior regions, most are found anterior to the molars. Occasionally, lesions are found on the edentulous areas of the alveolar ridges.

Lesions begin as a reddish or purplish dome-shaped swelling of the interdental papillae or alveolar



FIGURE 9-7
Peripheral giant cell granuloma. Lesions are commonly located in the interdental papilla.

ridge (Figure 9-7). In the dentulous patient they are often more reddish because of the ulceration that occurs when food is masticated and impinges on the thinned epithelium of the extruded mass. Larger lesions usually encircle one or more teeth, often involving the periodontal ligament, including the apex of the teeth (Figure 9-8, A). These lesions produce loosening and movement of the teeth. In the edentulous areas the lesions are domed, purple, and usually have an intact surface. A periapical radiograph commonly reveals a superficial saucer-shaped loss of cortical bone, and the more central area of the bone remains uninvolved.

HISTOPATHOLOGY

The microscopic appearance reveals a nodular arrangement of giant cell tissue separated by fibrous septa. The giant cell tissue consists of a mixture of mononuclear and multinucleated giant cells against a background of extravasated red blood cells (Figure 9-8, B). Some capillary vessels and sinusoidal spaces are usually present. The fibrous stroma may be loose or dense and contains large, thin-walled vascular structures. Heavy deposits of hemosiderin are common within the giant cell tissue and the surrounding fibrous component.

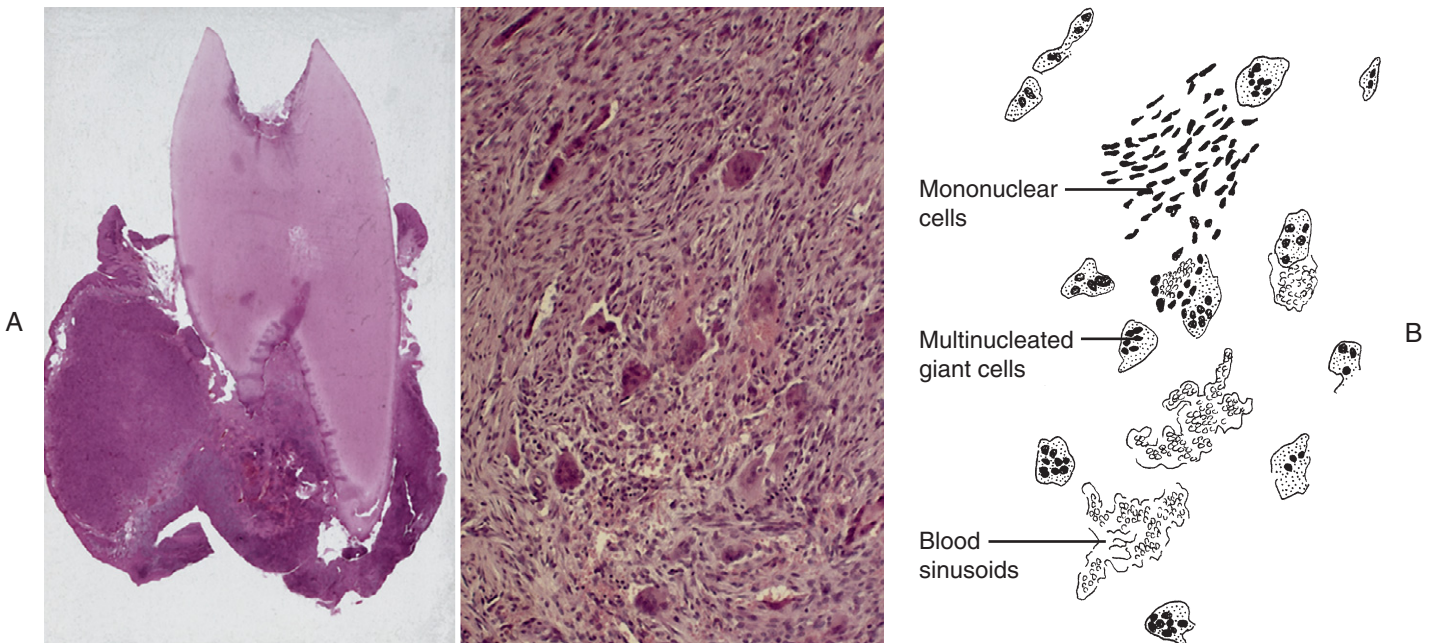


FIGURE 9-8
Peripheral giant cell granuloma. **A**, Low-power microscopy illustrating giant cell tissue within the periodontal membrane and surrounding the tooth. **B**, High-power microscopy and accompanying tracing of features of giant cell tissue illustrating the mononuclear and multinucleated giant cells and the irregularly shaped sinusoidal spaces.

TREATMENT

Peripheral giant cell granuloma is treated by surgical excision. Removal must include all the giant cell tissue, because recurrences are common. In the dentulous patient this usually requires removal of one or more teeth and curettage of the socket.

Inflammatory Fibrous Hyperplasia

INFLAMMATORY FIBROUS HYPERPLASIA: A proliferation of fibrous connective tissue with an associated chronic inflammation in response to chronic injury.

Ill-fitting dentures with overextended flanges or older dentures that irritate vestibular tissue after alveolar ridge resorption may stimulate fibroblastic proliferation and collagen synthesis. These hyperplastic processes are most frequently found adjacent to denture flanges and tend to be multilobulated and diffuse. When they result from the impingement of an overextended flange, lesions usually contain an elongated trough with a linear ulcer (fissure) at its base. In the past it was commonly referred to as *epulis fissuratum*.

CLINICAL FEATURES

Denture-induced fibrous hyperplasia is usually encountered in the maxillary or mandibular anterior vestibule where it is associated with an ill-fitting denture that has overextended denture flanges. The hyperplastic tissue is frequently lobulated or in folds and may be fissured where the denture flange impinges on the tissue at the base of the linear troughs (Figure 9-9). Most of these hyperplastic growths are erythematous because of the areas of ulceration. Occasionally they may be normal in color. They are consistently flabby, soft, and movable and may occur anywhere along the margins of the prosthesis; the anterior locations are most common.

HISTOPATHOLOGY

The surface stratified squamous epithelium is frequently hyperplastic, demonstrating acanthosis with elongated rete ridges. Occasionally, zones of ulceration are encountered and the ulcerated areas are occupied by fibrin with entrapped leukocytes. The bulk of the tissue is composed of mature, fibrous connective tissue that is hypocellular. Spindle-shaped fibroblasts are interposed between dense collagen fibers in a scarlike pattern (Figure 9-10). When the fibrous hyperplasia extends into the lip and buccal mucosa, minor salivary gland lobules may be identified and will usually show acinar degeneration and ductal dilatation with inflammatory cell infiltration (chronic sclerosing sialadenitis).

TREATMENT

Diffuse inflammatory fibrous hyperplasia associated with an irritating dental prosthesis will not resolve completely on its own, even if the denture irritation is corrected or the denture is withdrawn. Lesions often become smaller when the denture is withdrawn, altered, or rebased because of the reduction in the inflammation. The permanently formed fibrous component will remain, resulting in an irregular, unstable area of soft tissue. For new prosthetic appliances to be satisfactory, the residual fibrous masses must be excised in their entirety before fabrication of a new dental prosthesis.



FIGURE 9-9
Inflammatory fibrous hyperplasia. With the denture removed the lesion reveals two linear folds of hyperplastic connective tissue with a central trough that is frequently ulcerated, thus contributing to the often-accompanying intense inflammation. This lesion is commonly referred to as *epulis fissuratum*.

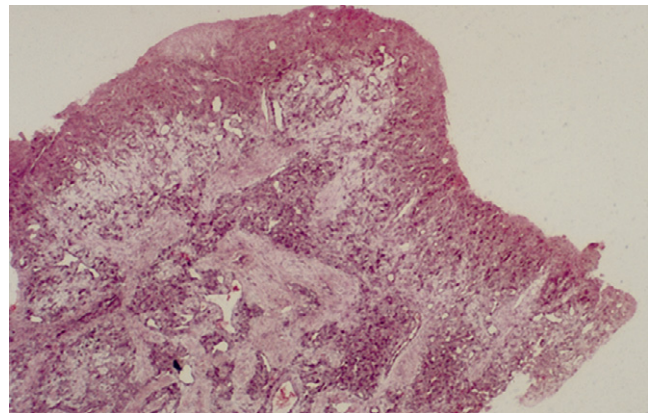


FIGURE 9-10
Inflammatory fibrous hyperplasia. Low-power microscopy exhibiting an abundance of dense fibrous connective tissue interspersed with focal accumulations of inflammatory cells and an increase in vascularity, all of which contribute to the excessive tissue.

Inflammatory Papillary Hyperplasia

INFLAMMATORY PAPILLARY HYPERPLASIA:

Multiple small nodules that consist of a proliferation of fibrous connective tissue with an associated chronic inflammation found under ill-fitting dentures.

Some loose and ill-fitting maxillary dentures will initiate a hyperplastic response on the tissue of the palatal vault. This response is even more intense in dentures that have been made with a so-called palatal relief, whereby negative pressure is placed against the palate. The palatal tissue responds by producing numerous small areas of erythematous focal fibrous hyperplasia that resemble the surface of a papilloma.

CLINICAL FEATURES

Inflammatory papillary hyperplasia is confined to the palatal vault, seldom progressing onto the alveolar ridge. This is an important clinical observation, because verrucous carcinoma, an aggressive epithelial proliferation, usually involves the alveolar ridge and vestibule and may extend to the palate, thereby resembling papillary hyperplasia. Inflammatory papillary hyperplasia is usually encountered under full dentures but occasionally occurs under the palatal coverage of partial dentures. The hyperplastic nodules are characteristically 3 to 4 mm in diameter, with a generalized erythematous “cobblestone” pattern resembling a field of confluent reddish-pink mushrooms (Figure 9-11). When probed with a dental instrument, it can be seen that each polyp is independently attached.



FIGURE 9-11

Inflammatory papillary hyperplasia. The lesion occurred under a denture that had been ill fitting for a prolonged period. The erythematous densely compacted nodules near the midline of the hard palate give the tissues a “cobblestone” appearance.

HISTOPATHOLOGY

Tissue sections disclose an obvious polypoid appearance with multiple smooth, round nodules covered with stratified squamous epithelium. Where two papillary projections meet at their base, the epithelium is usually quite hyperplastic and displays acanthosis with elongated, anastomosing rete ridges (pseudoepitheliomatous hyperplasia). The individual epithelial cells fail to show any atypical cytologic features. The hyperplastic response is not confined to the connective tissue but also involves the overlying epithelium. Supporting each polypoid projection is a dense core of fibrous connective tissue that is traversed by capillaries. Scattered mononuclear inflammatory cells are usually dispersed throughout the connective tissue. This inflammatory component is quite variable and may be minimal in some cases.

TREATMENT

The hyperplastic tissue should be removed before fabrication of a new maxillary partial or complete denture. This may be achieved with a scalpel, a fluted burr on a rotary instrument, electrocautery, or laser surgery.

Hyperplastic Gingivitis

HYPERPLASTIC GINGIVITIS: *Focal or generalized fibrous hyperplasia of the marginal gingiva with an associated inflammatory response.*

Although the gingiva may be edematous and somewhat enlarged in chronic gingivitis and periodontal disease, it rarely becomes conspicuously enlarged. Such an occurrence is referred to as *hyperplastic gingivitis* and represents an exuberant inflammatory fibrous hyperplastic response (usually to calculus and plaque) that is often intensified by the patient's hormonal status.

CLINICAL FEATURES

A predilection exists for this form of gingivitis in females, because it is encountered with increased frequency during puberty and pregnancy (**puberty gingivitis**, **pregnancy gingivitis**). Conceptually it is postulated that hyperplastic gingivitis represents an excessive fibrous hyperplasia with an associated inflammatory cell infiltration that occurs in response to elevated estrogen and other hormone metabolites. The enlargements are centered in the interdental papillae where the tissue may be spongy and erythematous with a tendency to bleed with minimal provocation (Figure 9-12).

HISTOPATHOLOGY

The surface epithelium exhibits parakeratosis with marked acanthosis and epithelial hyperplasia characterized by elongated and anastomosing rete ridges.

**FIGURE 9-12**

Focal hyperplastic gingivitis. The lesion is typically an erythematous enlargement of the interdental papilla of the gingiva. Milder degrees of gingivitis may be present in other areas.

Transmigration by neutrophils into the epithelium is common. The submucosal connective tissue accounting for the zones of enlargement are represented by an unremarkable-appearing fibrous connective tissue with prominent vascularity. Disbursed throughout this tissue are mononuclear inflammatory cells—mainly plasma cells and lymphocytes. The clinical enlargement is due to both fibrous hyperplasia and mononuclear inflammatory cell infiltration.

TREATMENT

Dental prophylaxis with scaling and polishing may produce some resolution; however, the fibrotic gingiva usually fails to return completely to normal contour. Attempts to surgically remove the enlarged tissue will result in recurrence as long as the hormonal influences remain. In pregnancy gingivitis, definitive treatment should not be performed until after delivery. Persistent enlargement that interferes with function can be managed by gingivoplasty.

Hereditary Gingival Fibromatosis

HEREDITARY GINGIVAL FIBROMATOSIS: A hereditary form of generalized gingival hyperplasia in which the autosomal dominant form may be associated with hypertrichosis, craniofacial deformities, epilepsy, and mental retardation.

Diffuse gingival hyperplasia may occur as a hereditary disorder. Although the precise mechanism of the disease is unknown, it appears to be restricted to the fibroblasts that populate the gingiva. The hyperplastic response

does not involve the periodontal ligament and occurs peripheral to the alveolar bone within the attached gingiva. There appear to be at least two modes of inheritance: autosomal dominant and autosomal recessive. The affected DNA sequences have been identified.

CLINICAL FEATURES

The gingiva becomes markedly enlarged and may cover the crowns of the teeth (Figure 9-13). The autosomal dominant form is most often associated with hypertrichosis and other defects, including corneal dystrophy, craniofacial deformities, nail defects, and deafness. In the forms occurring in children, epilepsy and mental retardation are sometimes present. In the autosomal recessive form, facial anomalies with hypertelorism have been observed, but most forms are without defects other than the gingival enlargement. Consanguinity has been observed in the recessive forms of the disease.

In most patients the gingival enlargement begins at puberty and shows progressive proliferation that involves both the interdental papilla and the attached gingiva. Lingual and labial gingiva tissues may be involved. Clinically the gingiva is bulbous, firm, and hard, yet it usually retains its normal coloration. No sex predilection exists. The gingival enlargement is usually minimal but may be massively fibrotic, covering the crowns of the teeth. Eruption of teeth is normal.

HISTOPATHOLOGY

The surface epithelium exhibits elongated, thin rete ridges. The fibrous connective tissue is densely collagenous, with scattered mature spindle-shaped fibroblasts. Significant numbers of mast cells exist that

**FIGURE 9-13**

Hereditary gingival fibromatosis. The gingiva is firm, normal in color, and exhibits a generalized overgrowth that in some areas exceeds the height of the crowns of the teeth.

are associated with the fibroblastic proliferation. Inflammatory cells are essentially lacking. The tissue reaction is usually indistinguishable from other forms of gingival fibromatosis, including those associated with medications.

TREATMENT

Gingivectomy is the treatment of choice for patients in whom the gingiva becomes massively enlarged and covers the clinical crowns. After surgery the tissue will recur but may take many months or even years to reach the massive size observed in patients who develop severe forms of the disease. Better oral hygiene practices do not appear to influence the degree of hyperplasia.

Drug-Induced Gingival Hyperplasia

DRUG-INDUCED GINGIVAL HYPERPLASIA: A generalized increase in the fibrous component of the gingiva in patients who have been taking long-term doses of phenytoin, cyclosporine, and nifedipine.

The three pharmaceutical agents that most commonly have an effect on gingival fibroblast proliferation are phenytoin (Dilantin); cyclosporine; and nifedipine, a calcium channel blocker. Persistent dental plaque and gingival irritation appear to increase the severity of the hyperplasia.

CLINICAL FEATURES

The gingival enlargement encountered because of Dilantin and nifedipine are clinically similar. They tend to begin in the interdental area involving the papilla and

progressively enlarge until the crown is obscured (Figure 9-14). Clinically, the enlargement is diffuse and firm. Inflammatory changes are variable and the enlargement appears to be more severe among patients who do not maintain good oral hygiene. Cyclosporine is frequently administered as an immunosuppressive agent in transplant patients. The hyperplasia associated with this drug is usually less severe than that encountered with Dilantin and nifedipine. The gingiva may assume a multinodular or papillary appearance. In most instances drug-induced gingival hyperplasia becomes obvious within the first year of drug administration. As the gingival enlargement progresses, periodontal **pseudopockets** form around the crowns of the teeth. The disease is restricted to the gingiva when Dilantin and nifedipine are the associated agents. In addition to the gingiva, cyclosporine is known to induce fibrosis in other organ systems, including the retroperitoneum and the kidneys.

HISTOPATHOLOGY

The microscopic features of drug-induced gingival hyperplasia are similar to those seen in hereditary gingival fibromatosis. The epithelium is thin and the rete ridges are markedly elongated and delicate, showing anastomosis. The connective tissue is composed of dense mature collagenous fibers with widely dispersed spindle-shaped fibroblasts (Figure 9-15). Inflammatory infiltration is variable, usually depending on the extent of the patient's oral hygiene.

TREATMENT

Most patients cannot withdraw their medication, and therefore local treatment must be provided. Gingivectomy and gingivoplasty are often required for functional



FIGURE 9-14

Drug-induced gingival hyperplasia. Patient with generalized gingival hyperplasia as the result of the administration of cyclosporine.

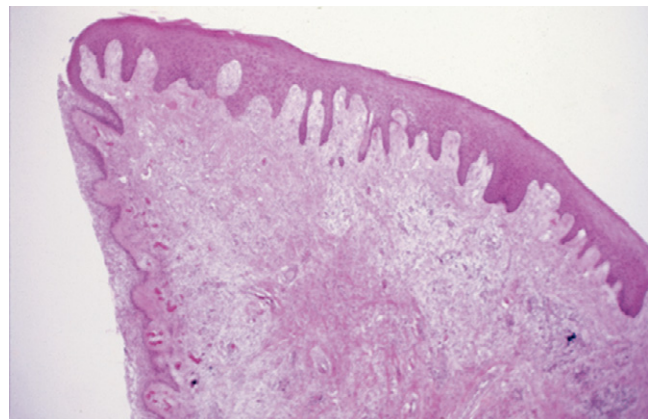


FIGURE 9-15

Drug-induced gingival hyperplasia. Microscopic features reveal elongated sulcular epithelium (*left side*) and hyperplasia as the result of excessive production of dense bundles of collagen in a scarlike pattern.

and cosmetic reasons. The fibrotic changes will slowly recur. Because the recurrence rate is accelerated by the accumulation of plaque and calculi, regular dental prophylaxis and rigid home care are mandatory.

BENIGN FIBROUS NEOPLASMS

Fibromatosis, myofibromatosis, nodular fasciitis, and fibrous histiocytoma are considered benign neoplasms of fibroblastic or myofibroblastic connective tissue cells. Although these tumors histologically resemble the fibrous proliferations that arise in reaction to injury, they are more aggressive; some proliferate rapidly, becoming large and displacing significant portions of normal tissue. Although the lesions are aggressive and locally destructive, they do not metastasize. They are characterized by a cellular proliferation of fibroblasts and the elaboration of collagen fibers. It is the large increase in the number of fibroblasts, referred to as *hypercellularity*, which distinguishes this group of lesions from the more innocuous reactive fibrous hyperplasias that have been discussed previously.

Fibromatosis, Myofibromatosis, Myofibroma, and Desmoplastic Fibroma

FIBROMATOSIS: A benign diffuse infiltrative proliferation of fibroblasts and mature collagen occurring within the soft tissues of the head and neck in young patients.

MYOFIBROMATOSIS AND MYOFIBROMA: A benign diffuse infiltrative proliferation of myofibroblasts and mature collagen occurring within the soft tissues of the head and neck in young patients.

DESMOPLASTIC FIBROMA: A benign diffuse infiltrative proliferation of fibroblasts or myofibroblasts and mature collagen occurring primarily within the mandible in young patients.

The **fibromatoses** may occur anywhere in the body, yet certain sites such as the palms of the hands and the lateral neck are favored locations. A fibromatosis of the oral soft tissue is uncommon, compared with the other reactive fibrous hyperplasias that are attributed to chronic irritation. These fibrous proliferations may be comprised of fibroblasts, contractile fibroblasts (myofibroblasts), or a combination of both cell types.

Myofibroma is a solitary localized tumor, whereas **myofibromatosis** is more diffuse and may occur in multiple sites in a single patient. The fibromatosis occurring within the bone of the mandible is a distinct, aggressive proliferation that has also been termed **desmoplastic fibroma** of bone.

CLINICAL FEATURES

Fibromatoses tend to occur in patients during the first and second decades of life; however, some are present at birth. No significant sex predilection exists. In the neck they appear as nodular masses within the deeper tissue, usually on either side of the sternomastoid muscle. They tend to grow slowly but sometimes show rapid enlargement. On palpation they are firm and may be movable. Some are markedly indurated and run the entire length of the lateral neck. When a neck lesion occurs bilaterally, it is referred to as **torticollis**. Individuals suffering from this form of fibromatosis appear to have a webbed neck.

Similarly, fibromatosis of the oral soft tissues is an aggressive lesion that can become large in a short period. Lesions in this area are firm, usually diffuse, and fixed to the surrounding tissue. They may involve the buccal mucosa, tongue, and submandibular regions. Most fibromatoses of the oral regions arise in the cheek or in the submandibular areas. When adherence to the mandibular periosteum occurs, it is common to have superficial erosion of the underlying bone (Figure 9-16).

Central (intraosseous) fibromatosis of the jaws is often referred to as **desmoplastic fibroma of bone**. Similar to soft tissue fibromatoses, the central fibrous proliferations arise in young patients and are aggressive. They cause bony expansion, displacement of the teeth, and resorption of the roots. Radiographically a unilocular or multilocular radiolucency is observed, and the margins of the radiographic defect are usually relatively well demarcated. The midbody and inferomedial aspect of the ramus of the mandible are the most common locations for this tumor.

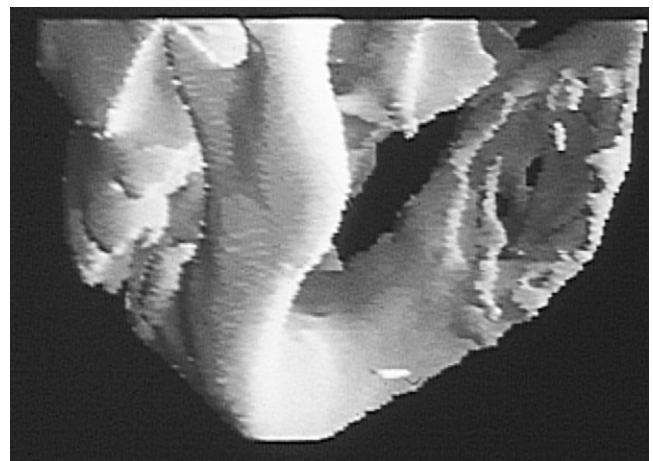
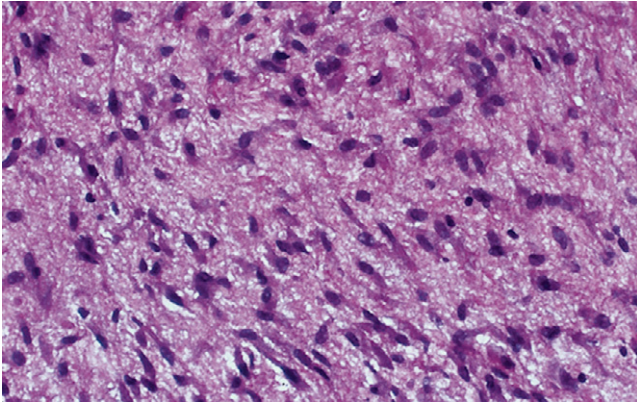


FIGURE 9-16

Oral fibromatosis. Three-dimensional computed tomography of the mandible, illustrating the erosion of the lingual cortical plate resulting from an adjacent fibromatosis in a young patient.

**FIGURE 9-17**

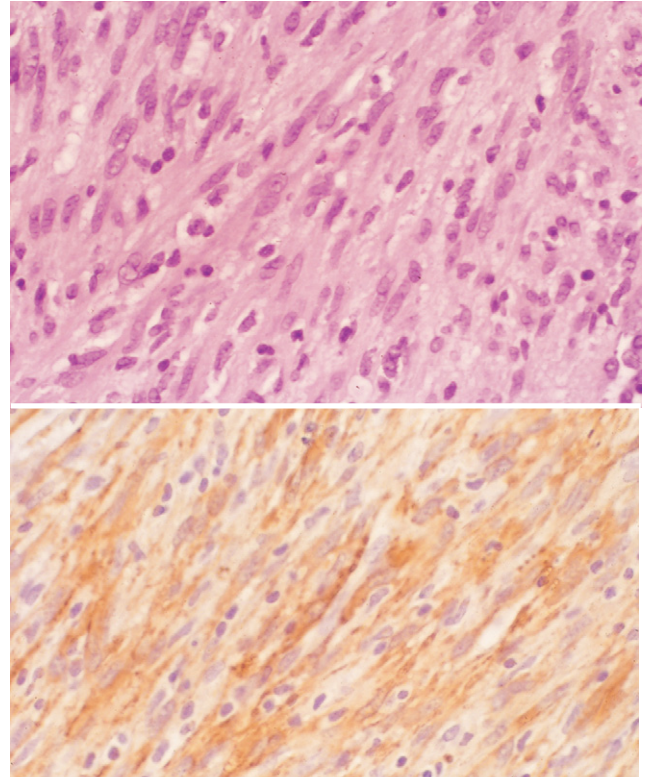
Oral fibromatosis. Microscopic features illustrating the uniform pattern of abundant spindle-shaped fibroblasts and mature collagen.

HISTOPATHOLOGY

Fibromatosis is characterized by a hypercellular proliferation of fibroblasts with accompanying mature collagen fibers. The individual fibroblasts are monomorphic, elongated, and typically spindle shaped (Figure 9-17). Cytologic atypia and mitotic activity are not encountered. The cellularity may predominate, and the elaboration of the collagenous product may be a relatively minor component. The collagen fibers are relatively thick and mature. In other lesions or even other fields of the same lesion, the collagenous component is more prominent and has a desmoplastic (scarlike) appearance. In myofibromas and myofibromatoses, the nuclei are elongated, yet they have blunt ends yielding a cigar-shaped appearance (Figure 9-18, A). They are further characterized by immunohistochemical markers for smooth muscle actin as detected by immunoperoxidase staining of the tumor tissue (Figure 9-18, B). Fibromatoses may be relatively well demarcated; however, they are not encapsulated; most tumors will infiltrate into neighboring muscle and other connective tissue, giving the impression of invasion. In torticollis of the neck, desmoplasia is a frequent feature.

TREATMENT

The behavior of these lesions varies depending on the site. Tumors arising in the lateral neck show continued proliferative capabilities, whereas in torticollis the proliferation appears to slow down and even arrest after puberty. Fibromatoses and myofibromatoses behave similarly and are treated the same. A solitary fibromatosis and a myofibroma are usually treated by a wide local excision to include normal adjacent tissue. Twenty-five percent of the tumors treated in this manner will recur. In the mandible the affected teeth must be extracted before the tumor is removed by curettage. Large expansile lesions require en bloc resection.

**FIGURE 9-18**

Myofibromatosis. **A**, The tumor is hypercellular with blunt-ended spindle nuclei and thin, wavy collagen fibers. **B**, Smooth muscle actin immunoreactivity highlights the contractile proteins of the myofibroblasts.

Nodular Fasciitis

NODULAR FASCIITIS: A localized, benign lesion composed of fibroblasts and myofibroblasts that is often clinically mistaken for a malignancy.

Also termed *pseudosarcomatous fasciitis*, nodular fasciitis represents a benign fibroblastic proliferation of the soft tissue. It exhibits unique microscopic features that allow differentiation from other fibroblastic proliferations. Nodular fasciitis is more commonly encountered in the extremities, with about 15% to 20% appearing in the head and neck regions.

CLINICAL FEATURES

Within the oral cavity the lesion appears as a rapidly growing, firm, submucosal mass. Despite its rapid onset, its growth potential is limited. It may arise elsewhere within the upper respiratory system and the parotid gland. No sex predilection exists, and the average age of a patient is 35 years. On palpation the tumor is firm, may be painful when compressed, is usually less than 5 cm in diameter, and may even appear to be partially encapsulated. In most

instances nodular fasciitis is a submucosal mass with a normal-appearing surface; some may have an ulcerated surface (Figure 9-19).

HISTOPATHOLOGY

Confusion with fibrosarcoma is the most frequently encountered problem with nodular fasciitis, because the cells exhibit some degree of pleomorphism and hypercellularity. The primary cell type is spindle or stellate in shape, with the tissue demonstrating a tendency for a fascicular or swirled arrangement. Tissue spaces filled with extracellular mucin that have a myxoid appearance are prominent (Figure 9-20). Multiple mitotic figures may be encountered. In some instances multinucleated giant cells are present. Despite the high cellularity, individual nuclei are essentially monomorphic and uniform in appearance. Immunocytochemical marker studies indicate that most of the fibroblastic cells are myofibroblasts,



FIGURE 9-19
Nodular fasciitis. An ulcerated mass of the buccal mucosa.

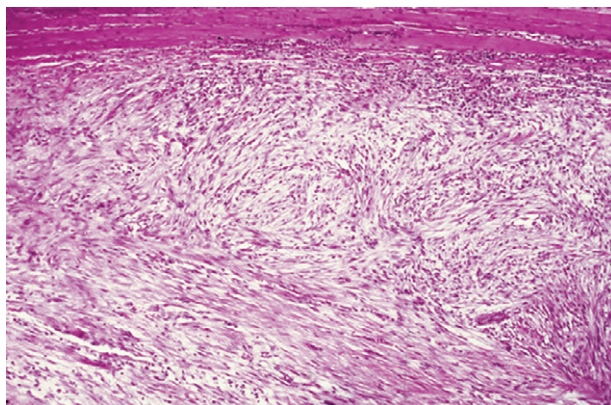


FIGURE 9-20
Nodular fasciitis. Low-power microscopy reveals a capsulelike outer boundary and a fibrous lesion containing abundant spindle and stellate cells against a slightly myxoid (loose) background with mucinous tissue spaces.

because they stain positively for muscle-specific actin, smooth muscle actin, and vimentin.

TREATMENT

Local excision is the treatment of choice. Local recurrences have been recorded but are uncommon. Those that recur do so within a few months of the initial surgery and are usually the result of an incomplete excision.

Benign Fibrous Histiocytoma

BENIGN FIBROUS HISTIOCYTOMA: A benign neoplasm of fibroblasts with a propensity to differentiate into histiocytes.

A benign fibrous histiocytoma is a fibrous proliferation that exhibits histiocytic differentiation. These lesions can be quite aggressive and are considered to represent true benign neoplasms of facultative fibroblasts. Facultative fibroblasts are mesenchymal cells that have the potential to differentiate into both fibroblastic and histiocytic cells. Some sources contend that benign fibrous histiocytomas are reactive proliferations, whereas others consider them benign neoplasms. A malignant variant is recognized.

CLINICAL FEATURES

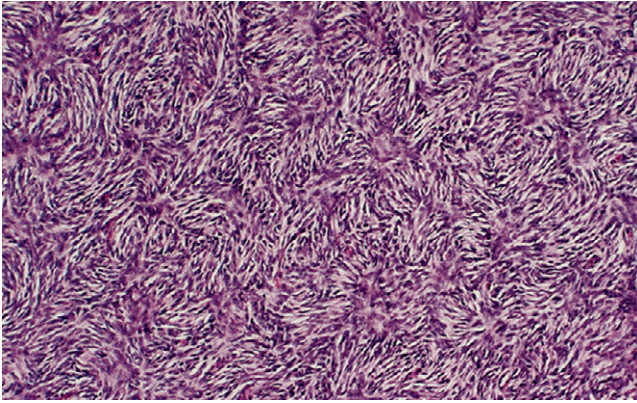
Benign fibrous histiocytoma occurs anywhere in the head and neck area, including the soft tissue of the oral region. It is usually well demarcated and movable yet firm or even indurated on palpation (Figure 9-21).

HISTOPATHOLOGY

Fibrous histiocytoma is composed of elongated, spindle-shaped fibroblasts that elaborate mature collagen and large cells with oval nuclei and copious amounts of cytoplasm representing histiocytes. The borders are often



FIGURE 9-21
Benign fibrous histiocytoma. Radiograph of lesion overlying the zygomatic process.

**FIGURE 9-22**

Benign fibrous histiocytoma. Tissue exhibiting the storiform pattern of the spindle-shaped fibroblasts and mature collagen.

infiltrative yet may be partially encapsulated or well delineated. The tumor cells are arranged in fascicles and whorls and are often tightly interwoven with hypercellularity. Those lesions located more superficially within the tissue will frequently show fibroblastic cellular arrays that resemble a pinwheel. This is referred to as a *storiform pattern* and is characteristic of fibrohistiocytic lesions. In other tumors the fibroblastic element is more loosely arranged and forms alternating fascicles and whorls (Figure 9-22). Mitotic figures are uncommon. Interposed among the fibroblastic elements, often in isolated groupings, are histiocytic cells, which may show pleomorphic nuclei. Some of these cells have intensely stained cytoplasm and may be multinucleated; others have foamy cytoplasm because of the presence of intracytoplasmic lipids. These latter cells are referred to as *xanthoma cells*.

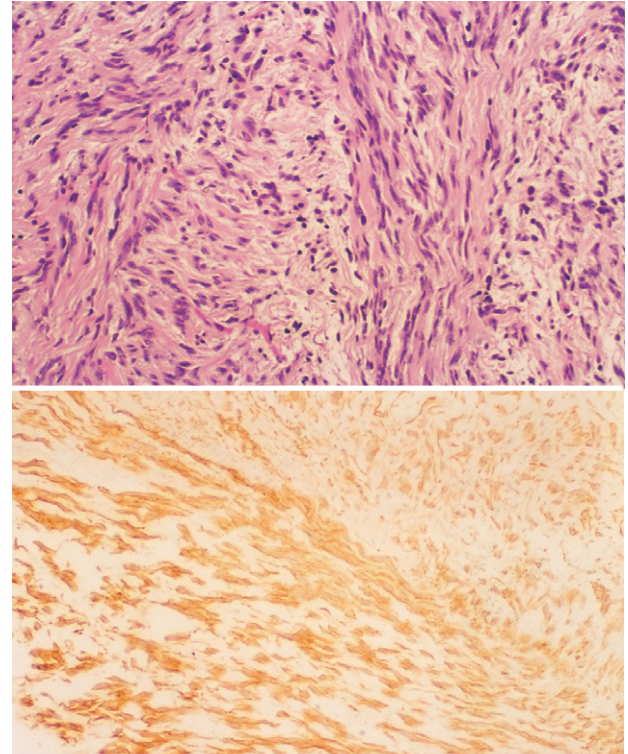
TREATMENT

Fibrous histiocytoma is an aggressive proliferation that may become multinodular and reach a large dimension. Some appear to be self-limiting in their growth potential. Wide local excision is the treatment of choice; approximately 20% will recur within the first 2 years.

Benign Solitary Fibrous Tumor

BENIGN SOLITARY FIBROUS TUMOR: A benign neoplasm of fibroblastic cells with production of collagen that is hypercellular and typically labels with the CD 34 histochemical marker.

The previously discussed benign fibroblastic proliferations are simply fibroblastic or myofibroblastic; in contrast, the solitary fibrous tumor is a proliferation of fibroblastic cells that bear the CD 34 marker, a cell surface protein that is found on specialized fibroblasts that envelop skin appendages and some hematopoietic cells.

**FIGURE 9-23**

Solitary fibrous tumor. **A**, Fibroblasts and collagen fibers arranged in a wave pattern. **B**, CD 34–positive immunostaining of neoplastic fibroblasts.

CLINICAL FEATURES

These fibrous tumors are uncommonly encountered in the oral regions. Most appear as firm, movable submucosal nodules in the buccal mucosa yet may occur in the lips and tongue. They most frequently occur during midlife, and a female predilection exists.

HISTOPATHOLOGY

The tumor is comprised of slender fibroblasts with collagen fibers that range from delicate to mature. The loose myxoid regions as seen in nodular fasciitis are not seen in solitary fibrous tumor. The tissue is hypercellular and the cells are monomorphic, lacking mitotic activity. They are often said to be patternless, because they do not show any distinctive growth pattern that may be encountered in other fibroblastic or neurofibroblastic tumors. One distinct feature, however, is a tendency for the cells and accompanying collagen to form tight wave-like ribbons (Figure 9-23, A). As mentioned previously, this tumor is positive for CD 34 protein, a marker that is found on hematopoietic cells, endothelial cells, and periadnexal fibroblasts of skin (Figure 9-23, B).

TREATMENT

This benign tumor is treated by local excision, and recurrences are uncommon.

MALIGNANT FIBROUS NEOPLASMS

Fibrosarcoma, Malignant Fibrous Histiocytoma, and Malignant Solitary Fibrous Tumor

FIBROSARCOMA: A malignant neoplasm of fibroblastic cells.

MALIGNANT FIBROUS HISTIOCYTOMA: A malignant neoplasm of fibroblasts with a propensity to differentiate into histiocytic and fibrohistiocytic cells.

MALIGNANT SOLITARY FIBROUS TUMOR: A malignant neoplasm of fibroblasts that demonstrate a patternless histopathologic picture and label with the CD 34 marker.

When fibroblasts become malignant, the resulting lesion is aggressive and destructive and is referred to as a *fibrosarcoma*. In some cases the malignant fibroblasts differentiate along histiocytic lines, and the tumor is termed a *malignant fibrous histiocytoma*; in malignant solitary fibrous tumor, the cells often label with CD 34.

CLINICAL FEATURES

In the head and neck region, fibrosarcoma, malignant fibrous histiocytoma, and malignant solitary fibrous tumor occur most frequently in the neck, but they also occur within the oral soft tissue, where they may involve the gingiva (Figures 9-24 and 9-25), tongue, buccal mucosa, or floor of the mouth. No sex predilection exists. The age distribution varies between these three tumors,

because fibrosarcomas tend to occur in children; middle-aged adults are more often affected by malignant fibrous histiocytoma and malignant solitary fibrous tumor. These tumors are rapidly proliferating and are firm and indurated on palpation. They lack encapsulation and become fixed to adjacent tissue. Larger lesions may be associated with ulceration of the surface epithelium.

Both fibrosarcoma and malignant fibrous histiocytoma can arise within bone. Fibrosarcomas are more often encountered within the mandible, where they appear as sharply defined radiolucencies. Root resorption, tooth displacement, and cortical expansion are frequent. Malignant fibrous histiocytoma is the most common sarcoma to involve the maxillary sinus. Lesions are thought to arise from fibrohistiocytic cells within the submucosal lining of the sinus. Malignant fibrous histiocytoma is rarely found within the mandible.

HISTOPATHOLOGY

Fibrosarcoma is a highly cellular tumor composed of anaplastic spindle-shaped nuclei with an eosinophilic cytoplasm that blends with delicate collagen fibers. Mitotic figures are numerous, and many are atypical (Figure 9-26, A). The cells are arranged in fascicles, often with a “herringbone” pattern. The high mitotic rate and hypercellularity distinguish this lesion from other benign fibroblastic tumors.

Malignant fibrous histiocytoma is a highly pleomorphic fibroblastic tumor composed of spindle cells and a mixture of pleomorphic and multinucleated cells with copious eosinophilic cytoplasm. Foam cells may also be identified. The nuclei show marked pleomorphism, high mitotic activity, and bizarre or atypical mitotic

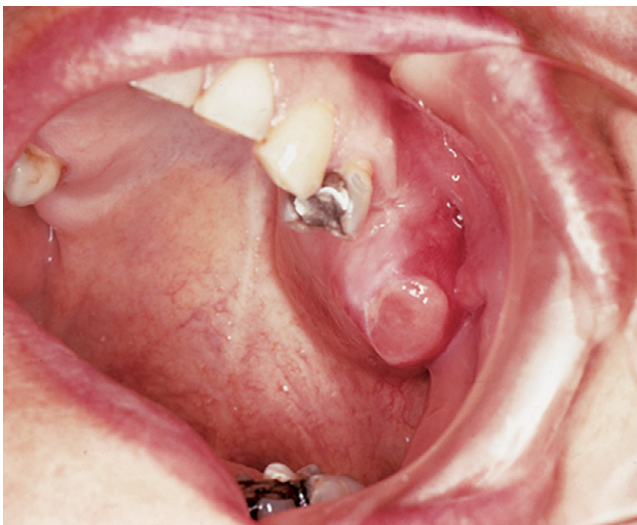
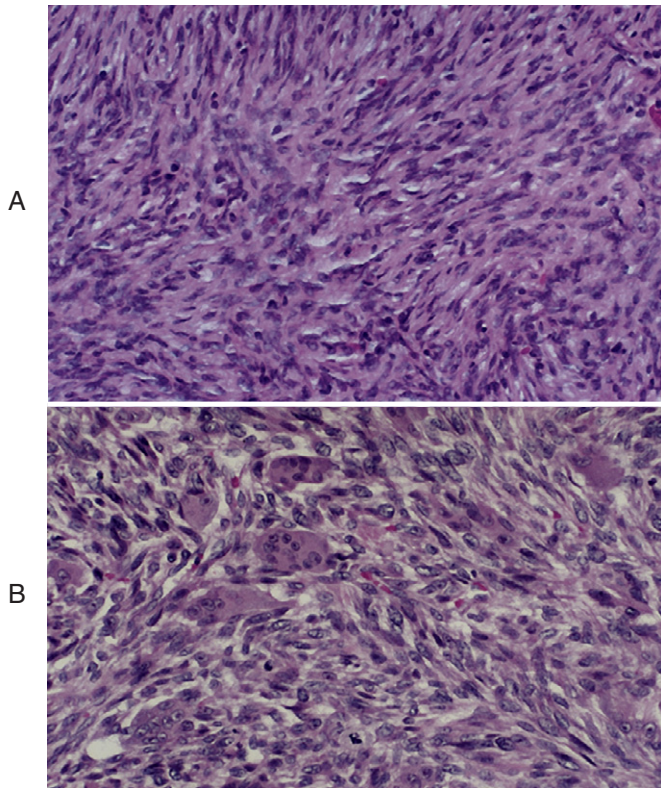


FIGURE 9-24
Fibrosarcoma. Extraosseous lesion of the posterior left maxillary gingiva.



FIGURE 9-25
Malignant fibrous histiocytoma. Lesion of the posterior left alveolar ridge, exhibiting ulceration.

**FIGURE 9-26**

A, Fibrosarcoma. Medium-power microscopy consisting of anaplastic spindle cells in a “herringbone” pattern. **B, Malignant fibrous histiocytoma.** Pleomorphic and multinucleated spindle cells and abnormal mitotic figures are exhibited.

figures (Figure 9-26, B). Fibrosarcoma and malignant fibrous histiocytoma lack a capsule and show borders that infiltrate adjacent tissue.

Like its benign counterpart, malignant solitary fibrous tumor is a cellular patternless tumor of fibroblastic cells that frequently label with immunoperoxidase staining for CD 34. In this malignant form, nuclear pleomorphism and mitotic figures are observed.

TREATMENT

All three of these fibroblastic malignancies are aggressive, rapidly proliferating tumors that tend to metastasize to distant sites through vascular routes. Regardless of the therapeutic regimen, the prognosis is generally not good. Radical wide excision is the treatment of choice. In the jaws, radical resection is recommended.

NEURAL TISSUE

The head and neck area contains the highest concentration of sensory nerve fibers of any location in the body. Reactive and neoplastic proliferation originating from the

cells that ensheath the neural axis cylinder are relatively common within the oral cavity and neck. When nerve fibers are injured, they undergo wallerian degeneration, whereby the distal axis cylinder segment degenerates and the proximal segment attempts to reroute itself through the existing Schwann cell sheath. This regeneration phenomenon is uncomplicated when the proximal segment is able to track itself into a juxtaposed distal nerve sheath. Alternatively, when the two ends are displaced, or lost completely as occurs with an amputation, a reactive hyperplasia of nerve and accompanying Schwann cells may develop during the futile attempt to rejoin with the distal nerve sheath. This hyperplastic response is termed *traumatic* or *amputation neuroma*.

The benign neoplasms derived from the cells that constitute the nerve sheath include neurilemoma and neurofibroma. Not only do these tumors arise from the nerve sheath, but also differentiate in a manner that emulates the cells from which they were derived. The axis cylinder is enveloped by Schwann cells that form a continuous layer around the axis cylinder, much like insulation around an electric wire. These Schwann cells are capable of synthesizing myelin, which contributes to the insulating effect of the sheath.

The neoplasm that is derived from the Schwann cell is the neurilemoma. The neuroectodermal tissue cells that synthesize collagen and create a binding network that envelops all of the individual axis cylinders with their associated Schwann cells are referred to as *perineural fibroblasts*. Within the nerve proper, these cells resemble fibroblasts and constitute the endoneurium. These same cells, or their derivatives, also form an outer sheath around the entire nerve, referred to as the *perineurium*. These perineural fibroblasts are thought to give rise to the neurofibroma. The granular cell tumor, common in the tongue, may also arise from nerve sheath cells, although the sarcolemma of skeletal muscle may also be the cell of origin.

Most oral nerve sheath tumors are located in the tongue; however, because nerves are present throughout the oral cavity, any mucosal site may be affected. In the head and neck areas, nerve tumors are most commonly located along the course of the auditory nerve in the temporal bone or in the lateral neck. Whereas most of these tumors are solitary, neurofibromas can be multiple, constituting the syndrome referred to as *multiple neurofibromatosis* or *von Recklinghausen disease*.

HYPERPLASIA

Traumatic Neuroma

TRAUMATIC NEUROMA: A painful nodular proliferation of nerve and fibrous tissue of the nerve sheath resulting from the futile attempt of nerve fibers to reunite with their severed distal portion.

Traumatic neuroma, also referred to as *amputation neuroma*, evolves when a nerve is severed and the proximal segment seeks to reunite with the distal nerve sheath in the process of regeneration. When the two nerve segments are displaced, the proximal segment undergoes axis cylinder elongation with the accompanying nerve sheath, which includes both Schwann cells and perineural fibroblasts. This vain attempt to reunify with the distal segment results in a tortuous proliferation of nerve tissue that clinically appears as a submucosal fibrous mass.

CLINICAL FEATURES

Within the oral cavity the most common site for traumatic neuroma is along the distribution of the mental nerve, particularly in the area around the mental foramen (Figure 9-27). Usually a history of laceration or



FIGURE 9-27

Traumatic neuroma. Lesion located over the mental foramen is usually firm and painful when palpated.

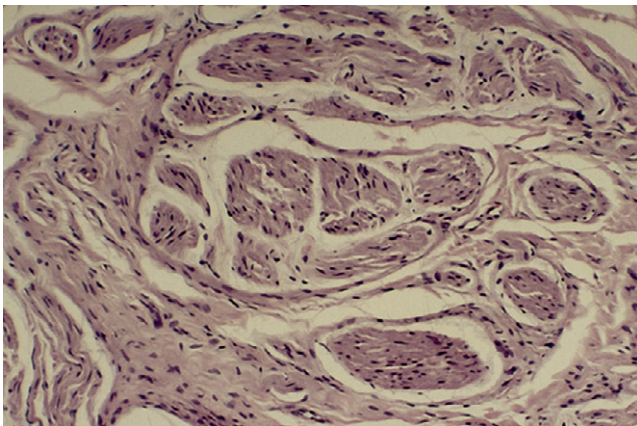


FIGURE 9-28

Traumatic neuroma. Medium-power microscopy reveals tortuous nerve bundles separated by dense fibrous connective tissue (scar tissue).

trauma to the area exists. Traumatic neuromas in the neck may occur after trauma or surgery. The submucosal or subcutaneous neuroma is usually firm and painful on palpation. These hyperplastic nerve nodules are usually well encapsulated and movable within the underlying tissue.

HISTOPATHOLOGY

Because traumatic neuroma represents a hyperplasia of normal nerve and neural sheath elements, the microscopic features closely resemble that of normal nerve tissue and fibrous tissue, which are present in abundance. Multiple nerve bundles can be identified with axis cylinders, associated Schwann cells, and an enveloping perineurium. These nerve bundles are oval or elongated, tortuous, and separated from one another by mature fibrous connective tissue (Figure 9-28). Silver stains can be used to disclose the presence of axis cylinders.

TREATMENT

Because traumatic neuromas are often painful, surgical excision is recommended. A diagnosis cannot be based on clinical features alone but requires histopathologic examination. Simple surgical excision is the treatment of choice. Although recurrence is possible, most such lesions do not recur after complete excision.

Palisaded Encapsulated Neuroma

PALISADED ENCAPSULATED NEUROMA: A benign hyperplastic proliferation of neurites and nerve sheath cells that are enveloped by a well-defined perineural capsule.

Many believe that the palisaded encapsulated neuroma is a variant of traumatic neuroma. They are, in fact, more commonly encountered in the oral cavity and lips than are classic traumatic neuromas. Palisaded encapsulated neuroma has been suggested to arise from tactile end organ fibers (Meissner corpuscles).

CLINICAL FEATURES

This type of neuroma is most frequently found on the palate, lips, and anterior tongue areas that are subject to trauma. In men, nicks from shaving may be of causative significance in the upper lip, where they appear as well-defined subcutaneous pearly nodules (Figure 9-29). On the lips and in the oral mucosa, most of these neuromas are small, usually 5 to 10 mm in diameter, and they are superficially located, just underneath the epithelium. Some are painful when squeezed or palpated.

HISTOPATHOLOGY

The histologic features of palisaded encapsulated neuroma are distinctive and are characterized by a proliferation of spindle cells that are monomorphic and may



FIGURE 9-29
Palisaded and encapsulated neuroma. A pearly nodule of the upper lip is exhibited.

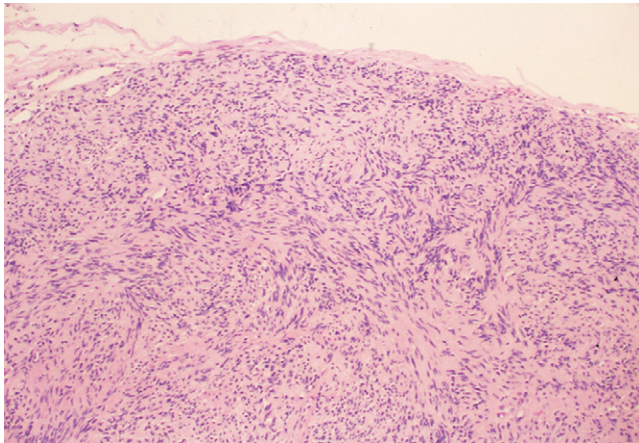


FIGURE 9-30
Palisaded and encapsulated neuroma. Microscopy reveals a well-demarcated lesion comprised of parallel strands of palisading spindle cells with delicate collagen fibers.

show a tendency for juxtaposed parallel alignment of nuclei known as *palisading*. In other areas of the proliferation, the cells are haphazardly arranged. The collagen fibers are wavy and delicate. A fibrous capsule that resembles perineurium envelopes these nerve sheath cells (Figure 9-30). Glial fibrillary acid protein and S-100 protein are positive immunomarkers.

TREATMENT

These small nodules are easily removed by simple excision, or they may be enucleated from the surrounding submucosal connective tissues. They do not tend to recur.

HAMARTOMAS

Multiple Endocrine Neoplasia Syndrome

MULTIPLE ENDOCRINE NEOPLASIA SYNDROME:

An autosomal dominant condition involving the parathyroids, pancreas, thyroid, and adrenals, with one variant (MEN-IIB) that has an oral manifestation consisting of multiple neuromas on the mucosal surfaces, lips, and anterior dorsal tongue.

Syndromes consisting of multiple neoplasms involving different endocrine glands are inherited as an autosomal dominant trait. These syndrome complexes are collectively referred to as *multiple endocrine neoplasia syndrome* (MEN). Hyperplastic proliferations or malignant neoplasms may involve various endocrine tissues, including parathyroid, pancreas, thyroid, and adrenal tissues. Only the variant of the MEN syndrome categorized as MEN-IIB exhibits oral manifestations. Patients with this variant of the syndrome develop malignant neoplasms, specifically a calcitonin-secreting medullary carcinoma of the thyroid gland and a catecholamine-secreting pheochromocytoma of the adrenal medulla. These endocrine tumors arise in association with the multiple mucosal neuromas that occur within the oral cavity and in the region of the eyelids.

CLINICAL FEATURES

MEN-IIB is usually inherited as an autosomal dominant trait and has been associated with a mutation on chromosome 10. Occasional sporadic cases are also encountered. The oral neuromas appear as multiple submucosal nodules, revealing a smooth surface and measuring less than 1 cm in diameter. These nodules are located in the submucosa of the upper and lower lips and on the anterior aspect of the tongue (Figure 9-31). Similar nodules may be encountered in the palpebral submucosa. These neuromas are hamartomatous nodules of neural tissue, and once they grow to a given size, they stop growing. Importantly, the oral neuromas are a harbinger for the development of endocrine neoplasia in the thyroid and adrenal glands. The neuromas usually occur during childhood, whereas the thyroid and adrenal tumors evolve during the second decade. The thyroid and adrenal tumors are malignant and have a potentially fatal outcome. When pheochromocytoma reaches a threshold size, catecholamine secretion will account for symptoms of episodic hypertension, cardiac palpitations, and facial flushing.

HISTOPATHOLOGY

The mucosal neuromas of MEN-IIB are remarkably similar in their microscopic appearance to traumatic neuroma. Intact nerve fibers represented by axis cylinders and accompanying Schwann cells are enveloped within

**FIGURE 9-31**

Multiple mucosal neuromas. Multiple small submucosal nodules of nerve tissue with smooth surfaces are present on the lips and tongue in patients with multiple endocrine neoplasia–IIB syndrome.

a single perineural capsule. Nerve clusters are separated from one another by mature fibrous connective tissue. The nerves of the neuromas of MEN-IIB are less tortuous than those of the traumatic or amputation neuroma; however, the two lesions may appear remarkably similar. Therefore the diagnosis is often based on the clinician's ability to detect multiple lesions on the lips, within the oral cavity, and on the eyelids.

TREATMENT

The mucosal neuromas are self-limiting hamartomatous lesions that usually require no treatment. Removal may be indicated for cosmetic reasons or when nodules interfere with mastication and speech. The recognition of the syndrome and the detection of the potentially fatal endocrine neoplasms of adrenal and thyroid glands is most important. These tumors are generally detectable using imaging techniques. Surgical treatment is indicated.

BENIGN NEOPLASMS

Neurilemoma

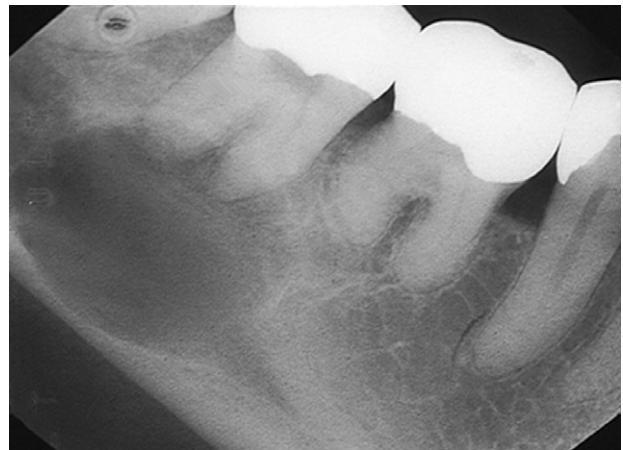
NEURILEMOMA: A well-demarcated, benign lesion consisting of a fibroblastic proliferation of the nerve sheath cell (Schwann cell) producing distinctive patterns referred to as Antoni A and Antoni B tissue.

CLINICAL FEATURES

Neurilemmomas typically occur as smooth, firm, raised, movable nodules within the oral soft tissue. They are common on the dorsal surface of the tongue (Figure 9-32). Lesions may also arise from the inferior alveolar nerve as a central lesion of the mandible. Central neurilemoma of the jaws presents as an expansile,

**FIGURE 9-32**

Neurilemoma. The dorsal surface of the tongue is a common intraoral location of this raised, firm, and movable lesion.

**FIGURE 9-33**

Intraosseous neurilemoma. Radiograph of lesion that is well demarcated and centered over the inferior alveolar nerve.

well-demarcated radiolucency (Figure 9-33) centered on the inferior alveolar nerve. Large lesions may be multiloculated and cause tooth root divergence and bony expansion. Neurilemmomas of the acoustic nerve, commonly referred to as *acoustic neuromas*, will often cause hearing loss. On the other hand, neurilemmomas arising within the connective tissue of the neck may become large yet do not elicit pain, sensory deficit, or paralysis.

HISTOPATHOLOGY

Neurilemmomas are composed of collagenous products. Myelin is not present, because no axis cylinders exist to induce myelin formation by the neoplastic Schwann cells. Lesions are well defined with the presence of a true capsule or a pseudocapsule of fibrous connective tissue. The basic cell is spindle-shaped with an elongated nucleus.

The cytoplasm cannot be readily delineated, because it blends in with the surrounding tissue. Two distinct patterns are pathognomonic for neurilemoma: The first pattern is referred to as the *Antoni A* tissue, which is represented by parallel rows of palisading nuclei. Frequently, two palisaded configurations are separated from one another by a cell-free zone, which is characterized by linear paralleling arrays of collagen fibers. These unique configurations are arranged in organoid swirls and are referred to as *Verocay bodies* (Figure 9-34). The second pattern is the *Antoni B* tissue, which is characterized by oval nuclei with surrounding collagen and distinctly vacuolated extracellular spaces. The *Antoni A* tissue forms multiple nodules that are interspersed by the *Antoni B* tissue (Figure 9-35). In tumors of long standing, myxoid changes commonly occur along with perivascular hyalinization and nuclear pleomorphism. These elderly tumors are referred to as *ancient neurilemmomas*.

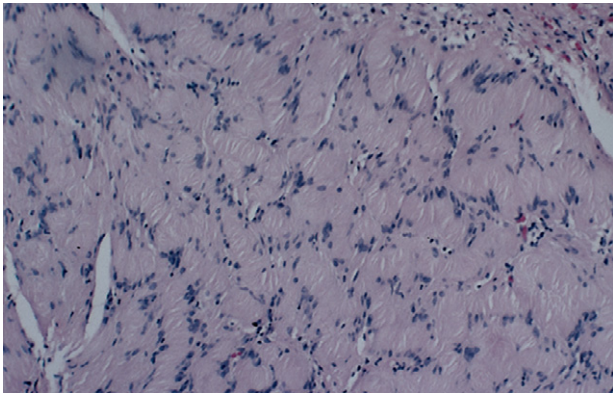


FIGURE 9-34

Neurilemoma. Medium-power microscopy features *Antoni A* tissue with its usual organoid pattern consisting of a central pink amorphous zone surrounded by palisaded spindle cells (Verocay bodies).

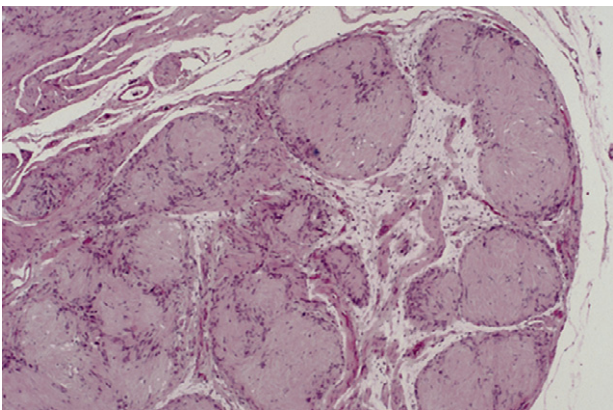


FIGURE 9-35

Neurilemoma. Low-power microscopy features *Antoni A* tissue (nodules) and *Antoni B* tissue (background loose myxoid tissue).

TREATMENT

Surgical excision is the treatment of choice for neurilemoma. Because tumors are well demarcated and encapsulated, they are easily dissected from the surrounding tissue. The recurrence for neurilemoma after excision or enucleation is less than 10%.

Neurofibroma

NEUROFIBROMA: A demarcated or diffuse benign proliferation of perineural fibroblasts that are oriented in either a random pattern with a myxoid background or a nodular (plexiform) pattern.

MULTIPLE NEUROFIBROMATOSIS: An autosomal dominant hereditary condition consisting of multiple neurofibromas of the skin and mucosa and associated café au lait pigmentations of the skin with the potential for producing disfigurement and malignant transformation.

The neurofibroma is derived from perineural fibroblasts and occurs with a variety of histologic subtypes. Some are diffuse and infiltrating, whereas others are multinodular and encapsulated. The majority of neurofibromas encountered within the oral cavity and neck are solitary. Occasionally, oral neurofibromas are a component of *multiple neurofibromatosis* (von Recklinghausen disease). This disease arises in patients who inherit a mutation in the NF gene, which encodes a tumor suppressor factor.

CLINICAL FEATURES

Within the oral cavity, neurofibroma is most frequently found in the tongue, followed by the buccal mucosa and the lips. Overall, solitary lesions of neurofibroma are most common on the skin (Figure 9-36). Most lesions are first noted in adults and show no sex predilection; they occur as relatively well-demarcated submucosal nodules.



FIGURE 9-36

Solitary neurofibroma. Lesion of the palmar skin that is raised, firm, and smooth surfaced.

Depending on the degree of collagenization, they may be soft or firm on palpation. In the buccal mucosa they are either localized and freely movable or soft and diffuse.

In multiple neurofibromatosis, neurofibromas may be encountered on both the skin and mucosal surfaces. Neurofibromatosis is inherited as an autosomal dominant trait with various subtypes. They are classified depending on the character and multiplicity of the tumors and the association with skin pigmentations. The neurofibromas in multiple neurofibromatosis may be nodular or diffuse. The nodular lesions vary in size from a few millimeters to many centimeters, are spherical,



FIGURE 9-37
Multiple neurofibromatosis. Patient has multiple soft intraoral lesions of the floor of the mouth, lingual gingiva, and right retromolar area.

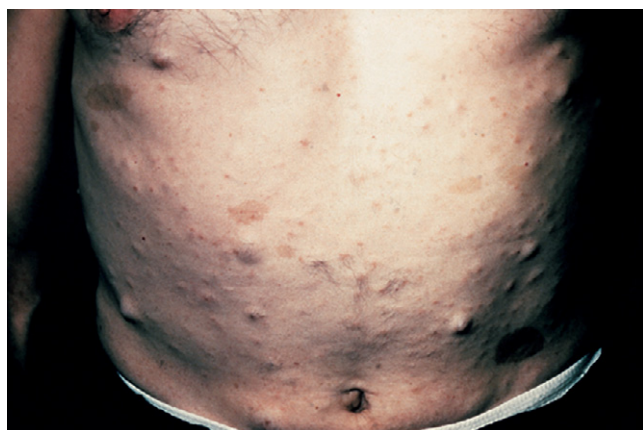


FIGURE 9-38
Multiple neurofibromatosis. Same patient as in Figure 9-32 with multiple neurofibromas and large, pigmented, macular lesions (café au lait spots).

and produce a domelike elevation of the skin. The number of tumors per patient will vary from several to hundreds. Within the oral cavity they are frequently present as multiple diffuse soft tissue enlargements (Figure 9-37). The diffuse form can be quite grotesque, with formation of pendulous tumor masses that may envelope an entire extremity. In the head and neck areas, tumors of this nature may result in massive, flabby, soft masses that emanate from the neck or involve the subcutaneous tissues of the face and scalp. This form of the disease has been publicized in the movie “The Elephant Man,” which is about such a patient; the name is now attached to the disease by laypersons. Another classic feature of the disease is the presence of one or more large, diffuse, macular, brown pigmentations on the skin, referred to as the café au lait spots (Figure 9-38). The macular pigmentations represent a focal increase in the synthesis of melanin similar to skin freckles or melanotic macules. Rarely are café au lait spots seen on the oral mucosa. Repeated surgical excision of a neurofibroma may predispose the site to a malignant transformation into neurogenic sarcoma. Indeed, approximately 6% of patients with multiple neurofibromatosis will manifest malignant nerve sheath tumors.

The mandible is the most common site for intraosseous nerve sheath tumors, referred to as **central neurofibroma**. No other bone in the skeleton contains a neurovascular bundle as long as that which is present within the mandible. The presence of an intraosseous central neurofibroma is rarely associated with paresthesia or pain. These tumors are usually brought to the attention of the patient by a swelling of the mandible. Some tumors are found when the



FIGURE 9-39
Intraosseous neurofibroma. Radiograph of a large, well-demarcated central (intraosseous) lesion of the posterior mandible that has displaced a molar.

clinician investigates a radiolucency observed during routine procurement of dental radiographs. Radiographically, the central neurofibroma is relatively well demarcated, radiolucent, and may be unilocular or multilocular (Figure 9-39). As the tumor expands, it may cause root divergence.

HISTOPATHOLOGY

A variety of histologic patterns are encountered in neurofibroma. The cells are spindle shaped and resemble fibroblasts. Haphazardly arranged spindle-shaped cells that elaborate a delicate collagenous product characterize the clinically diffuse lesions. The cells fail to show any specific orientation (Figure 9-40, A). In some tumors a ground substance is a prominent finding, yielding a myxoid appearance. Tumors of this nature are frequently

referred to as *myxoid neurofibromas* (Figure 9-40, B). Another variant is the **plexiform neurofibroma**. Multiple nodules of fibroblastic tissue with a prominent myxoid appearance characterize the plexiform variant. Each nodule appears to have a pseudocapsule resembling the perineurium.

When these encapsulated nodules are predominantly myxoid in appearance, the lesion is referred to as *nerve sheath myxoma*, or *neurothekeoma*. The plexiform and diffuse myxoid variants are seen in multiple neurofibromatosis. Central neurofibromas are more often fibromyxomatous, lacking the multinodular encapsulated foci typical of the plexiform variant. The café au lait pigmentations are represented by basilar melanosis without the proliferation of melanocytes.

TREATMENT

The solitary neurofibroma is usually managed by excision. Because many of these tumors are diffuse, lacking discrete encapsulation, wide excision (including adjacent clinically normal tissue) is the treatment of choice. Surgical removal of neurofibromas encountered in multiple neurofibromatosis may result in recurrence. Multiple recurrences have been associated with malignant transformation to neurogenic sarcoma. Therefore the neurofibromas in this condition are usually left untreated.

Granular Cell Tumor

GRANULAR CELL TUMOR: A submucosal mass consisting of diffuse sheets of large cells of either nerve or muscle origin, with a cytoplasm of densely packed eosinophilic granules (lysosomal bodies) and commonly found on the dorsal surface of the tongue.

Granular cell tumors are benign, submucosal neoplasms composed of large, oval cells containing prominent eosinophilic granules and small, round, monomorphic nuclei. Ultrastructural research has disclosed that the granules represent lysosomal or autophagic bodies. These cytoplasmic structures are ordinarily encountered in phagocytic cells and cells undergoing degeneration (but in small amounts). The derivation of granular cells has been controversial, with evidence supporting an origin from Schwann cells; another line of evidence supports derivation from skeletal muscle. Because these cells show no specific features of differentiation other than the accumulation of autophagic vacuoles, it may be that they can arise from either Schwann cells or the sarcolemma of skeletal muscle. Regardless of their origin, granular cell tumors are benign. Even though they lack encapsulation, they rarely recur after excision.

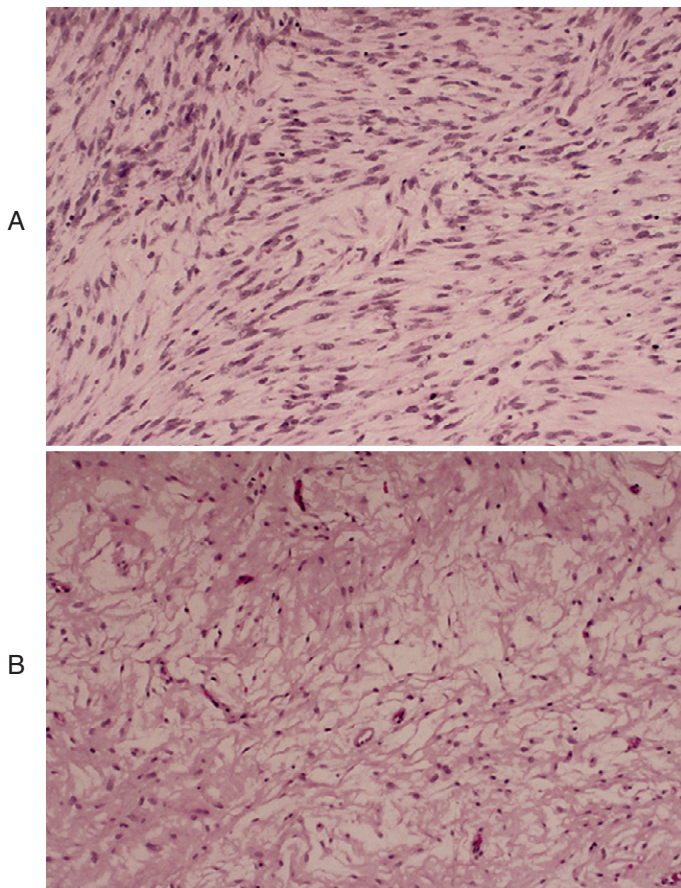


FIGURE 9-40

Neurofibroma. Medium-power microscopy features the two most common tissue patterns found in this lesion. **A**, Loose, delicate fibrous tissue containing haphazardly arranged spindle cells. **B**, Abundant mucinous ground substance with scattered spindle cells forming a myxoid connective tissue.

CLINICAL FEATURES

The granular cell tumor arises most frequently in the submucosa of the tongue, where it may be located in either the dorsal or lateral aspects (Figure 9-41). Uncommonly, it is also found on the ventral surface and in the soft palate. The lesion is extremely rare in other oral mucosal



FIGURE 9-41
Granular cell tumor. Lesion located on the left lateral border of the tongue is raised, firm, and smooth surfaced.

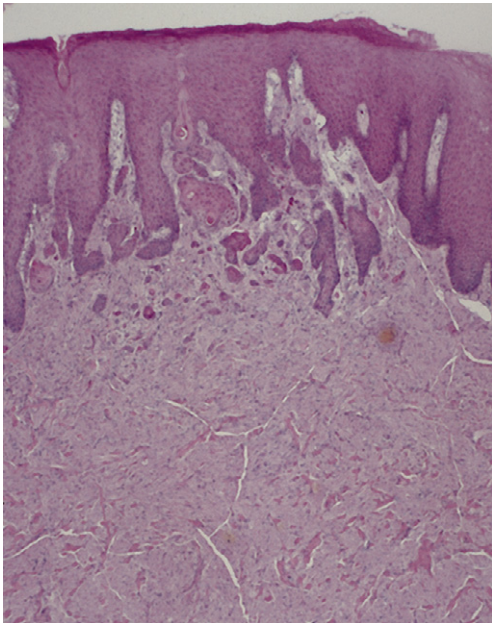


FIGURE 9-42
Granular cell tumor. Low-power microscopy of granular cells and overlying stratified squamous epithelium exhibiting pseudoepitheliomatosis hyperplasia.

sites. It is of interest to note that of all areas in the body, the tongue is the most common site for this unique tumor. In the tongue and the soft palate, a granular cell tumor presents as a firm, submucosal nodule or plaque, often with a yellow or orange tinge that is nonmovable and lacks encapsulation. The surface mucosa is usually intact; however, on the dorsum of the tongue, the usual tongue papillae may be replaced by a smooth (atrophic) mucosal surface. Men are more commonly affected than women. Rarely, multiple granular cell tumors may be encountered in the oral mucosa and on the skin.

HISTOPATHOLOGY

Within the submucosa are diffuse sheets of large oval cells with distinct cytoplasmic membranes and discrete, punctate, eosinophilic granules. These sheets of cells are well delineated but lack encapsulation. In most granular tumors the granular cells extend upward to the epithelium and are present between the rete pegs. It is not uncommon for an epithelial proliferation to occur in response to these cells. The response is referred to as *pseudoepitheliomatous hyperplasia* and is characterized by elongated and branched rete pegs resembling the pattern of a neoplastic growth (Figure 9-42). The epithelial cells lack cytologic atypia, a feature that differentiates this phenomenon from carcinoma. An erroneous diagnosis of squamous cell carcinoma has occasionally been rendered when insufficient submucosal connective tissue has been submitted for microscopic evaluation. Toward the inferior margin, continuity with the underlying skeletal muscle fibers is often apparent; frequently the granular cells appear to be emanating from individual skeletal muscle fibers. In other tumors the same granular cells are often found to emanate from nerve sheath cells. A small amount of fibrous stroma intervenes between the granular cells, although small vascular channels are present. When specific immunohistochemical markers are applied, the

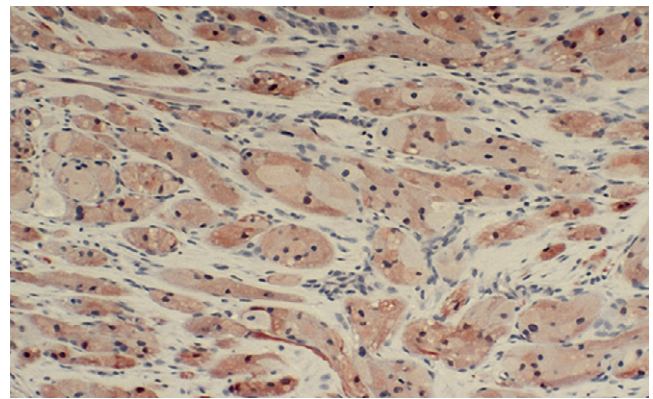


FIGURE 9-43
Granular cell tumor. High-power microscopy features granular cells intermingled with muscle cells and staining positive (brownish color) for S-100 protein.

granular cells are strongly positive for the S-100 protein (Figure 9-43), yet they often show positivity for skeletal muscle components, including actin and myoglobin.

TREATMENT

The granular cell tumor may be treated by simple local excision. Recurrence is rare.

Congenital Gingival Granular Cell Tumor

CONGENITAL GINGIVAL GRANULAR CELL TUMOR:

A pedunculated growth on the anterior maxilla or mandible of newborns that is composed of granular cells.



FIGURE 9-44

Congenital gingival granular cell tumor. A 7-day-old infant with a pedunculated, multilobular lesion of the anterior alveolar ridge.

The congenital gingival granular cell tumor is also referred to as *congenital epulis of the newborn* and *congenital granular cell epulis*. Although the cells appear to be similar to those of the granular cell tumor frequently found in the adult when viewed with light microscopy, some minor differences are seen when they are studied ultrastructurally and immunohistochemically. As with the granular cell tumor, the tissue of origin is still controversial.

CLINICAL FEATURES

Lesions are found only in the newborn, predominantly in the anterior maxilla (Figure 9-44), with occasional lesions in the anterior mandible. They occur far more frequently in females than males. The lesions are pedunculated, emanating from the crest of the alveolar ridge, have a smooth surface, and measure up to several centimeters in diameter.

HISTOPATHOLOGY

Contrary to the previously discussed granular cell tumor in adults, there is an absence of pseudoepitheliomatous hyperplasia of the overlying epithelium in the congenital gingival granular cell tumor, and the epithelium is usually atrophic (Figure 9-45, A). The lesion is composed of sheets of large cells with a granular cytoplasm and a vascular, noncollagenous stroma (Figure 9-45, B). Ultrastructurally, the congenital gingival granular cell tumor does not exhibit angulate bodies in the cytoplasm; however, both adult and congenital lesions contain autophagic vacuoles. Lesions are negative for the S-100 protein.

TREATMENT

Lesions are treated by surgical excision that includes the base of the stalk. Recurrences are rare.

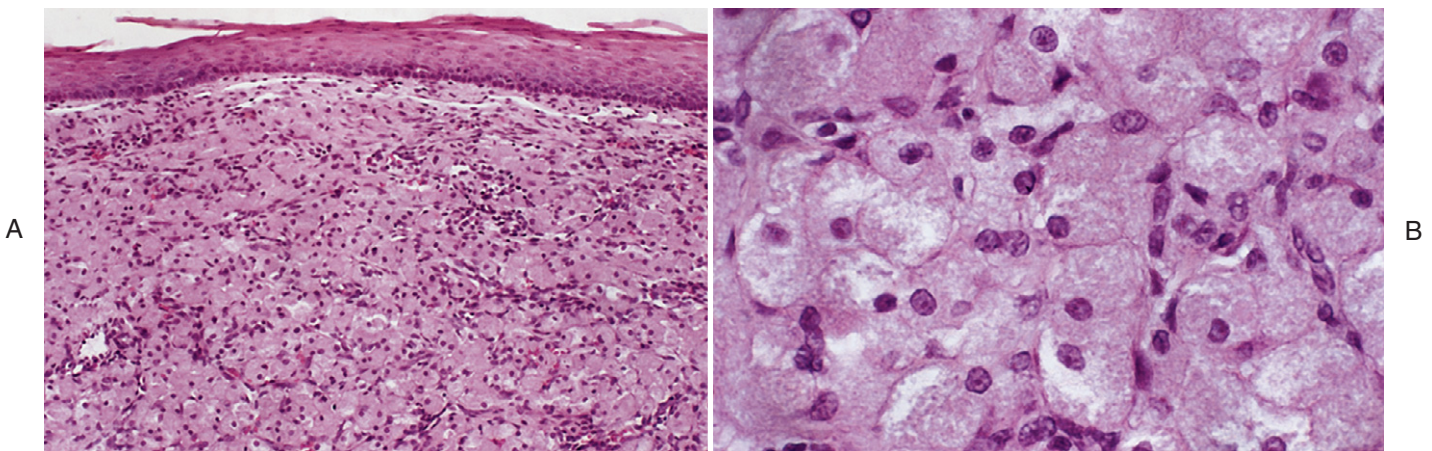


FIGURE 9-45

Congenital gingival granular cell tumor. A, Low-power microscopy of a lesion exhibiting a uniform pattern of granular cells with an outer surface of atrophic stratified squamous epithelium. B, High-power microscopy of large, rounded cells with granular cytoplasm and rounded nuclei.

Neuroectodermal Tumor of Infancy

NEUROECTODERMAL TUMOR OF INFANCY: A benign, usually pigmented neoplasm commonly of the anterior maxilla and composed of two cell types arranged in alveolar patterns and derived from embryonic neural crest tissue.

The neuroectodermal tumor of infancy is a benign congenital lesion derived from tissue of the primitive

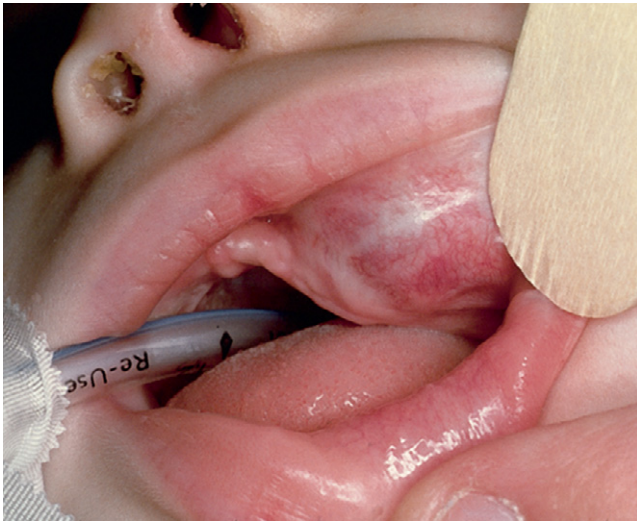


FIGURE 9-46
Neuroectodermal tumor of infancy. Lesion of a newborn producing a deformity of the anterior maxilla and lip. The mucosal surface exhibits a small amount of the pigmentation commonly found in these lesions. (Courtesy Dr. M. Rohrer, Dr. S. Young, and Dr. F. Rubin.)

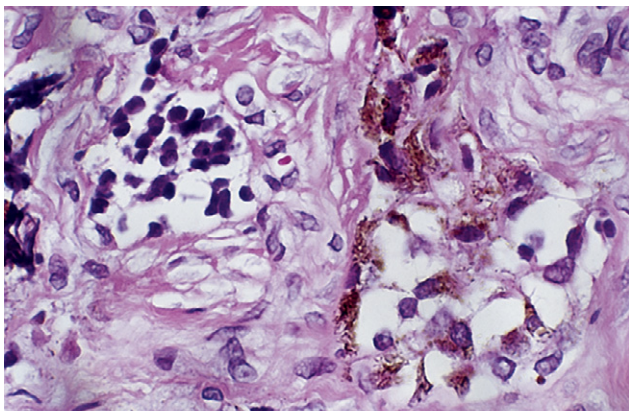


FIGURE 9-47
Neuroectodermal tumor of infancy. High-power microscopy exhibits two cell types arranged in alveolar patterns: (1) small, dark cells with a dense nucleus (*left*) and (2) large clear cells with open nuclei and producing melanin granules (*right*).

neural crest. Its true origin was not revealed until recently, when it was discovered that patients with lesions also had high urinary levels of vanilmandelic acid as is found in patients with neuroblastoma and pheochromocytoma, neoplasms of known neuroectodermal derivation.

CLINICAL FEATURES

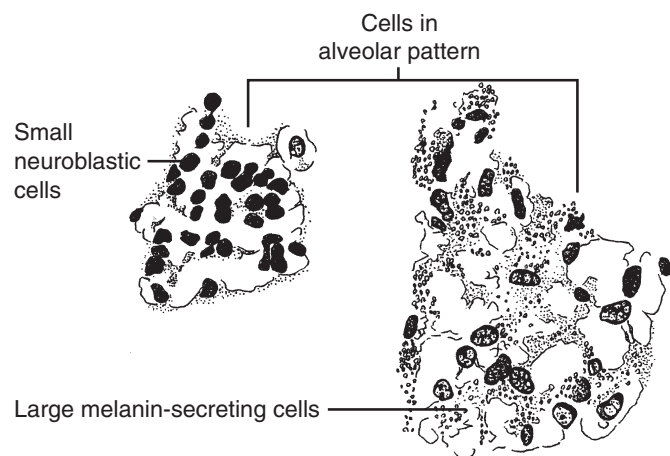
Lesions occur as pigmented swellings, commonly of the anterior maxilla. They appear in infants usually before the age of 6 months, presenting as an elevation of the lip. The surface may have a brown or black pigmentation, reflecting the melanin produced by the large cell component of the lesion (Figure 9-46). Radiographs often exhibit an intraosseous radiolucency with displacement of tooth buds. Approximately one fourth of the lesions found within the oral cavity occur in the mandible. Other sporadic locations include the shoulder, scapula, anterior fontanel, cerebellum, and mediastinum.

HISTOPATHOLOGY

The tissue is composed of two cell types against a dense fibrous connective tissue background. One type is large, with an open nucleus and a lightly staining cytoplasm that occasionally contains melanin granules. The other cell type is small, with a dark, dense nucleus and scant cytoplasm, resembling lymphocytes. The cells are commonly clustered and arranged in alveolar patterns (Figure 9-47).

TREATMENT

The neuroectodermal tumor of infancy is treated surgically and can be effectively eradicated with thorough curettage or conservative surgical resection. Recurrences are uncommon.



MALIGNANT NEOPLASM

Neurogenic Sarcoma

NEUROGENIC SARCOMA: A malignant neoplasm with a poor prognosis of perineural fibroblasts or Schwann cells, with a propensity to rapidly extend along the associated nerve trunk.

Although malignant nerve sheath tumors are occasionally encountered in the deep connective tissue of the neck, they are extremely rare in the oral cavity and jaws.

CLINICAL FEATURES

As mentioned previously, malignant transformation can occur in neurofibromas, particularly those that have been subjected to repeated surgical excision for recurrence in patients with multiple neurofibromatosis. Most malignant nerve sheath tumors of the head and neck regions are encountered in the deep soft tissue of the neck and arise *de novo*. Oral submucosal neurogenic sarcoma is extremely rare; but when such a tumor occurs, it grows rapidly and is indurated and nonmovable. Neurogenic sarcoma is more common within the mandible than in the soft tissue arising from the nerve sheath cells of the inferior alveolar nerve. Central neurogenic sarcomas of the mandible frequently extend along the inferior alveolar nerve, exiting through the lingula and superiorly toward the cranial base and Gasserian ganglion.

Radiographically, it frequently manifests as a fusiform widening of the inferior alveolar canal, as evidenced by a radiolucent appearance. Root resorption is not prominent. Clinically the patient may complain of paresthesia of the lower lip, and expansion of the mandible is usually observed.

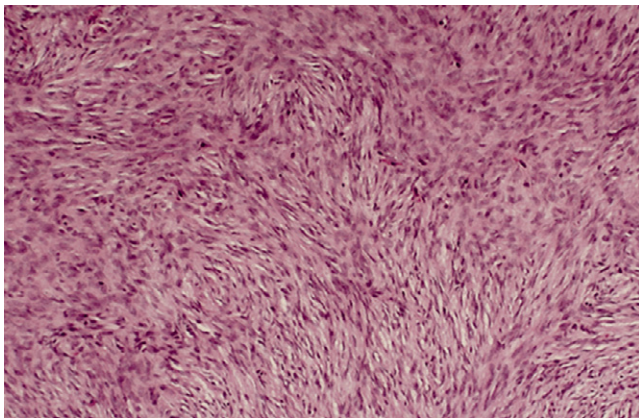


FIGURE 9-48
Neurogenic sarcoma. Medium-power microscopy reveals fascicles of malignant spindle cells resembling fibrosarcoma.

HISTOPATHOLOGY

Neurogenic sarcoma is characterized by a highly cellular tumor composed of fascicles of spindle-shaped nuclei (Figure 9-48). These fascicles sometimes show a resemblance to Antoni A tissue, but most are indistinguishable from fibrosarcoma. Therefore the diagnosis must be based on identifying that the tumor is in direct continuity with a nerve trunk. The nuclei are pleomorphic, and numerous mitotic figures are seen. An important feature of this lesion is the extension of the malignant neoplasm along the course of the involved nerve.

TREATMENT

Soft tissue neurogenic sarcoma must be treated by wide surgical excision. Local recurrence is a common complication, and hematogenous metastasis occurs in over 50% of the cases. Central neurogenic sarcoma of the mandible must be treated by mandibulectomy with wide excision and dissection along the nerve trunk up to the base of the skull. Despite aggressive surgery, local recurrence is common and distant metastases may ensue. The tumor is resistant to radiation therapy, and chemotherapeutic approaches have not proven effective.

MUSCLE TISSUE

Both benign and malignant tumors of muscle origin can arise within the oral cavity and in the regions of the head and neck, but they are uncommon. Only the granular cell tumor occurs with any degree of frequency in the tongue, and its origin from muscle cells is somewhat controversial. A true tumor of striated muscle occurs most frequently in the heart and is termed a *rhabdomyoma* (Figure 9-49); the tongue is the second most common site for this rare tumor. The other benign muscle

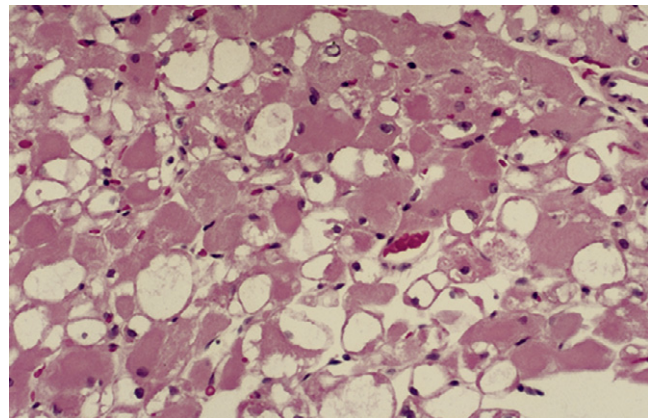


FIGURE 9-49
Rhabdomyoma. Medium-power microscopy of this rare benign neoplasm exhibits large round muscle cells rather than the elongated strap cells of normal muscle.

tumor, the *leiomyoma*, is derived from smooth muscle. These lesions are very common in the uterine cervix, where they are referred to as *fibroids*. Elsewhere in the body, most leiomyomas, including those within the oral cavity, arise from the smooth muscle surrounding arteries or arterioles. When origin from blood vessel walls is apparent, these lesions are referred to as **vascular leiomyomas**. Malignant neoplasms of either skeletal or smooth muscle are extremely rare within the oral cavity; however, when the malignancy of skeletal muscle (rhabdomyosarcoma) arises, it is usually in the periorbital tissue of children or the deep connective tissue of the neck in adults.

NEOPLASMS

Leiomyoma

LEIOMYOMA: *A benign neoplasm of smooth muscle within the oral cavity, usually of the blood vessels, that appears as a firm, movable, submucosal nodule.*

Leiomyomas are benign tumors of smooth muscle. Within the oral cavity they are usually derived from the smooth muscle component of the blood vessels.

CLINICAL FEATURES

Although the most common site within the oral cavity is the tongue, lesions also occur on the palate (Figure 9-50) and the lips. Leiomyoma arises during the adult years and has no sex predilection. In addition to the usual source of smooth muscle cells from the wall of blood vessels, it is conceivable that pleuripotential mesenchymal cells within the connective tissue may give rise to

this tumor. Leiomyoma is uncommon and usually appears as a smooth-surfaced submucosal nodule. The overlying epithelium lacks ulceration and may have a yellowish appearance. On palpation the tumors are firm and usually well delineated. In the loose tissues of the lip and buccal mucosa, they are freely movable.

HISTOPATHOLOGY

Leiomyomas are composed of spindle-shaped, smooth muscle cells with elongated nuclei that resemble fibroblasts. Because leiomyoma cells lack distinct cell margins, the cytoplasm of one cell appears to be fused to the adjacent cells. The elongated nuclei generally show blunt ends, resulting in a cigar-shaped appearance. These neoplastic cells are arranged in parallel fascicles, and lesions are either encapsulated or well delineated from the surrounding tissue. An intervening fibrous stroma is not evident, and only small capillaries are observed between the tumor cells. Differentiation from neurofibroma is often difficult. Because smooth muscle cells and fibroblastic cells are normally pink with routine hematoxylin and eosin (H&E) staining, applying a trichrome stain can assist in the differentiation of the two lesions. This latter stain differentiates the cytoplasmic elements of smooth muscle cells (pink) from the collagenous structures of fibroblasts (blue or green). Monoclonal antibodies to muscle-specific actin are also useful in confirming the diagnosis. Because most oral leiomyomas arise from perivascular cells, they show concentric laminations around endothelial-lined lumens (Figure 9-51). The vascular element is minimal, and the laminated smooth muscle cells dominate the histologic fields.

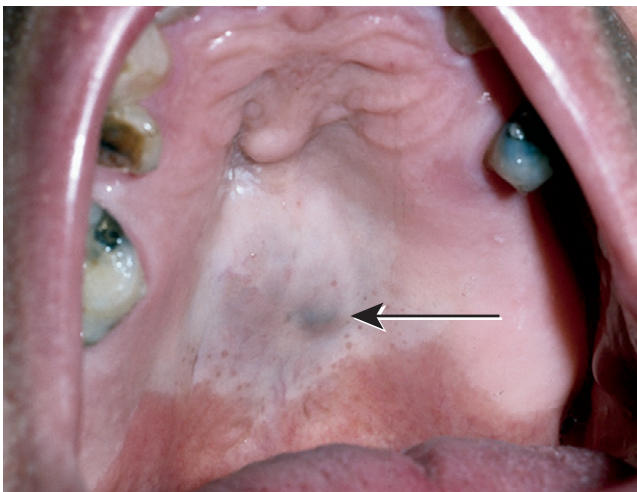


FIGURE 9-50

Vascular leiomyoma. The lesion is located on the palate as a firm submucosal swelling with a smooth intact surface.

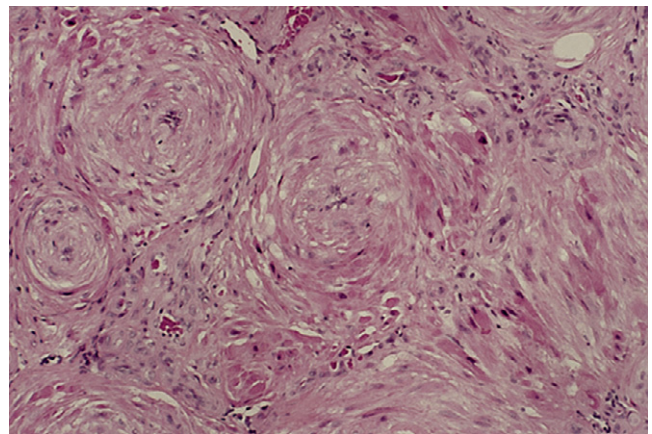


FIGURE 9-51

Vascular leiomyoma. Medium-power microscopy demonstrates the concentric laminations of smooth muscle cells around vascular channels that are nearly completely obliterated and a surrounding cellular fibrous connective tissue.

TREATMENT

Local excision, including adjacent normal-appearing tissue, is the treatment of choice. These benign, smooth muscle tumors rarely recur when completely excised.

Rhabdomyosarcoma

RHABDOMYOSARCOMA: A rare, rapidly growing malignant neoplasm of striated muscle that occurs in three histologic patterns (embryonal, alveolar, and pleomorphic); all have a poor prognosis.

Rhabdomyosarcoma is the malignant neoplasm of skeletal (striate) muscle. It is subcategorized into three microscopic variants, some of which arise in children and others in adults: The first variant, **embryonal rhabdomyosarcoma**, tends to arise in children and may be identified within the head and neck area. The second variant, **alveolar rhabdomyosarcoma**, is rarely seen in the oral region. The third variant, **pleomorphic rhabdomyosarcoma**, is more often encountered in adults, where the cells bear a close resemblance to skeletal muscle fibers. These neoplasms may arise from an existing skeletal muscle bundle or be derived from pleuripotential mesenchymal cells of connective tissue. In the latter case they are not necessarily localized within a muscle per se.

CLINICAL FEATURES

In the head and neck areas the periorbital region is the most common site for rhabdomyosarcoma. These tumors occur during childhood and are usually of the embryonal type. Both sexes are equally affected. These

tumors exhibit rapid growth, with displacement of the eye. The tumors are indurated, fixed, and frequently ulcerated. Pleomorphic rhabdomyosarcoma is more often encountered in adults and may arise within the oral cavity.

HISTOPATHOLOGY

Rhabdomyosarcomas are composed of malignant rhabdomyoblasts. The embryonal rhabdomyosarcoma is characterized by small round cells with hyperchromatic, relatively monomorphic-appearing nuclei. Mitotic figures are common. Around the periphery of the tumor the anaplastic rhabdomyoblasts become condensed, whereas in the central regions the tissue is looser. The cytoplasm is usually wispy and indistinct. Small capillaries course throughout the tumor. The *alveolar rhabdomyosarcoma* is so named because the rhabdomyoblasts form conglomerate groups that assume a pattern similar to the lung alveoli or organoid structures. Individual cells resemble the round cells seen in embryonal rhabdomyosarcoma.

Pleomorphic rhabdomyosarcoma is a more highly differentiated form, showing primitive muscle fiber formation. The nuclei are extremely pleomorphic and may contain prominent nucleoli. The tumor cells frequently assume a “tadpole” appearance, with a large pleomorphic nucleus and a brightly eosinophilic tail of cytoplasm (Figure 9-52). Many of these cells may show cross-striations that are demonstrated with a phosphotungstic acid–hematoxylin stain. Immunomarkers for skeletal muscle tumors, including desmin, muscle-specific actin, and myoglobin, stain positively in all three types of rhabdomyosarcoma.

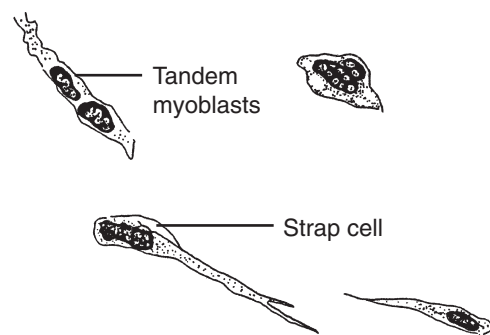
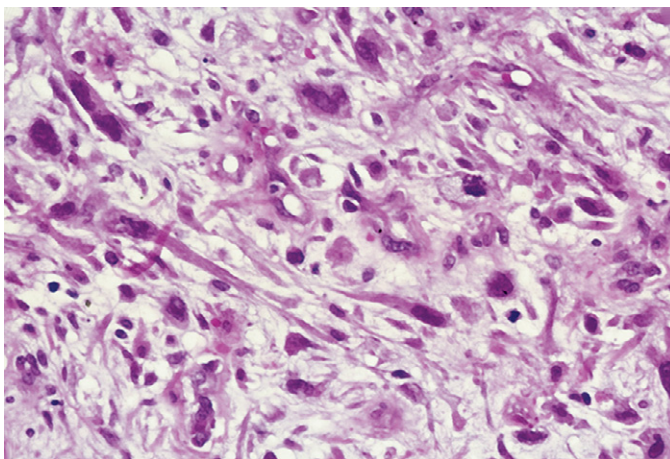


FIGURE 9-52

Rhabdomyosarcoma. Medium-power microscopy of the pleomorphic type of rhabdomyosarcoma exhibiting randomly distributed primitive and anaplastic muscle fibers, many of which are “tadpole-shaped” strap cells, whereas others are multinucleated with the cells in a linear pattern (tandem myoblasts).

TREATMENT

Rhabdomyosarcoma is a rapidly proliferating neoplasm with a marked tendency for hematogenous spreading and a poor prognosis. Embryonal rhabdomyosarcoma has a worse prognosis than the pleomorphic type. Surgery, radiation, and combination drug chemotherapy are the modalities used to treat these malignancies.

ADIPOSE TISSUE

Lipoma and liposarcoma are connective tissue tumors of adipose tissue origin. Lipoma is one of the most common benign neoplasms to arise in the neck and is frequently seen within the oral cavity. Lipoma is histologically identical to normal adipose tissue. Liposarcomas are rarely seen in the head and neck areas and are even rarer in the oral soft tissue.

NEOPLASMS**Lipoma**

LIPOMA: A benign neoplasm of normal fat cells that appears as a soft, movable swelling, often with a slight yellowish coloration.

The common lipoma is a benign neoplasm of adipose tissue composed of mature fat. Some variations exhibit more embryonic-appearing fat yet are still benign in nature. One such tumor occurs in multiple sites and is referred to as *multiple lipoblastomatosis*.

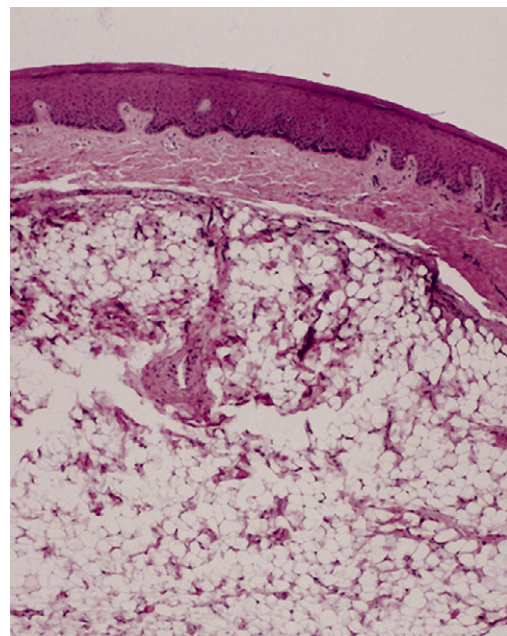
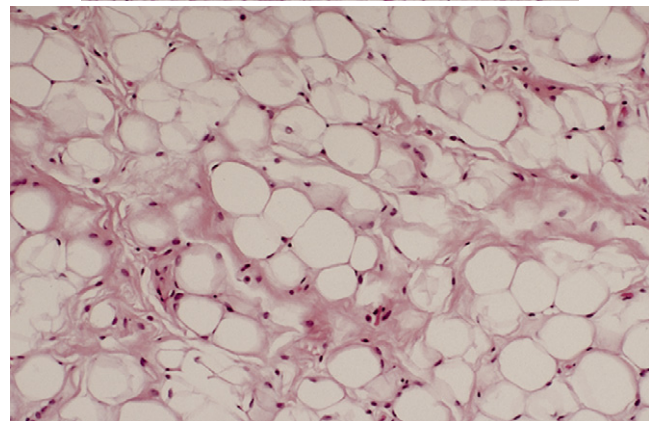
CLINICAL FEATURES

Lipomas are usually relatively well defined, soft on palpation, and freely movable within the underlying connective tissue. No sex predilection exists, and most lesions occur

in adults. In the neck they are usually encountered in the lateral regions along the sternomastoid muscle. Most oral lipomas arise within the superficial submucosal connective tissue (Figure 9-53). Some arise within the deeper tissue of the cheek and are detected only by palpation. The more superficial lipomas are often yellow and display a smooth overlying surface that may be telangiectatic. Fatty tissue within the buccal fat pad may herniate through the buccinator muscle. As the fatty tissue herniates through the damaged muscle fibers, it protrudes into the oral cavity as a buccal mucosal swelling. The **herniated buccal fat pad** reveals both clinical and histopathologic features that are indistinguishable from lipoma and are therefore diagnosed by obtaining a history of trauma.

**FIGURE 9-53**

Lipoma. The lesion is a soft, movable submucosal mass of right buccal mucosa.

**A****B****FIGURE 9-54**

Lipoma. **A**, Low-power microscopy demonstrates the sharply demarcated nodular mass of normal-appearing adipose tissue. **B**, Medium-power microscopy reveals the clusters of normal fat cells with the nuclei barely visible.

HISTOPATHOLOGY

Lipomas are distinctive on gross examination because they are yellow and float in aqueous solutions such as the formalin fixative. Lipomas are usually well defined, although they may not display a surrounding capsule. The adipocytes are identical to normal fat cells and exhibit a round, vacuolated clear cytoplasm with an eccentrically placed nucleus. Most lipomas have lobules of fat cells that are separated by fibrous septa (Figure 9-54). This same appearance is identifiable in herniated buccal fat pads. Occasionally, lipomas contain benign lipoblasts. These cells are characterized by a “soap bubble” appearance of vacuoles within the cytoplasm and multinucleated cells with nuclei arranged in a floret pattern. These are sometimes mistaken for malignant cells. This variant is referred to as *pleomorphic lipoma*. In some benign lipomas there may be significant amounts of myxomatous tissue in addition to the fat cells.

TREATMENT

Simple excision is the treatment of choice. Lipomas located deep within the tissue rarely recur after enucleation. Those arising in the submucosa of the oral cavity are usually treated by excision.

Liposarcoma

LIPOSARCOMA: A rare, malignant neoplasm of the oral cavity composed of a wide spectrum of histologic patterns of the fat cells.

Liposarcomas are usually encountered in the extremities and are infrequently observed in the head and neck regions. They are derived from cells that differentiate along adipose tissue lines and show some evidence of fat synthesis.

CLINICAL FEATURES

Malignant neoplasms with adipose tissue differentiation are usually multilobular and vary from firm to soft. Most patients have a history of rapid growth. Liposarcomas usually arise *de novo* rather than through a malignant transformation of a preexisting lipoma. In the head and neck areas, they are more often encountered in the deep tissue of the neck. Within the oral cavity they may arise in the sublingual or buccal mucosa regions.

HISTOPATHOLOGY

Morphologic patterns in liposarcoma vary widely, but the presence of lipoblasts is common to all. Some liposarcomas are composed of poorly differentiated round cells with only focal evidence of cytoplasmic vacuolization. Others display cells with a “signet ring” appearance in which the nucleus is prominently displaced to the side of a large vacuole. Some liposarcomas are

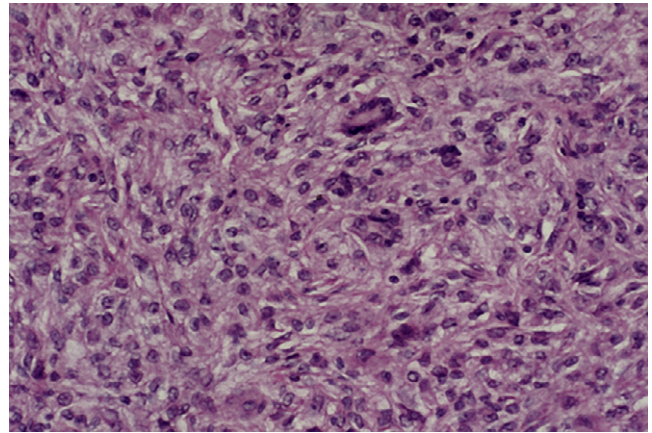


FIGURE 9-55

Liposarcoma. Medium-power microscopy exhibiting primitive lipoblasts with little evidence of fat production along with pleomorphic and multinucleated anaplastic cells.

highly anaplastic, whereas others show clear evidence of fatty differentiation (Figure 9-55).

TREATMENT

Like other sarcomas, liposarcomas tend to metastasize to distant sites such as the lungs, bone, and brain. The treatment of choice is surgical intervention with radical excision.

VASCULAR TISSUE

Most vasoproliferative masses within the oral cavity are forms of reactive granulation tissue in response to injury. The neoplasms are derived from the lining of the endothelial cells of blood vessels and are referred to as *hemangiomas*; those derived from lymphatic vessels are called *lymphangiomas*. Because hemangiomas are composed of numerous proliferating vascular channels containing erythrocytes, they usually appear clinically as red, purple, or blue lesions. Some hemangiomas are flat or macular, representing a superficial proliferation of vessels that fails to generate a tumefaction. Others are obvious swellings. Lymphangiomas contain lymphatic fluid, tend to be superficial, and appear as yellowish masses, whereas the less common deeper lesions are usually of normal coloration. Some hemangiomas lie deep within the tissue, particularly those that are interposed between muscle fibers, so-called *intramuscular hemangioma*. These lesions may have no discoloration of the surface mucosa or skin and are much more difficult to manage.

The mandible is the most common site in the body for vascular proliferations located within bone. These proliferations commonly evolve in patients early in life

and represent arteriovenous (AV) anastomoses in which an intervening capillary bed is lacking. Lymphatic malformations of a similar nature do not occur within the mandible or maxilla.

HYPERPLASIA

Pyogenic Granuloma

PYOGENIC GRANULOMA: *A fast-growing reactive proliferation of endothelial cells commonly on the gingiva and usually in response to chronic irritation.*

A focal reactive growth of fibrovascular or granulation tissue with extensive endothelial proliferation is termed a *pyogenic granuloma*. The term would imply that such lesions react to infection with pyogenic microorganisms. In fact, no relationship exists between bacteria and the emergence of these reactive proliferations. The tissue is infiltrated with many neutrophils, accounting for the erroneous interpretation of a bacterial cause. Pyogenic granulomas can occur anywhere in the body and are common on the fingers and toes around the nail beds. Within the oral cavity, pyogenic granulomas are frequently localized to the gingiva, where they are included as part of the differential diagnosis of an epulis. An *epulis* is a collective clinical term for focal growths of the gingiva. Trauma or introduction of foreign material into the gingival sulcus may provide the stimulus for this proliferative hyperplasia.

CLINICAL FEATURES

Within the oral cavity pyogenic granuloma is most often encountered in the interdental papilla region (Figure 9-56). These lesions may extend from the buccal to the lingual or palatal gingiva; however, they are most



FIGURE 9-56

Pyogenic granuloma. The erythematous exophytic lesion is located in the interdental papilla. In this location, it receives continuous chronic irritation, resulting in an ulcerated surface.

often limited to either the buccal or the facial surface. Because they are extremely vascular, they are usually fiery red and will often show a gray pseudomembrane over the surface, secondary to ulceration of the overlying epithelium. A significant female predilection exists, and lesions tend to occur more often during the second and third trimesters of pregnancy. These lesions are often referred to as *pregnancy tumors*. Although they are benign hyperplastic reactions, they may grow at an alarming rate, reaching 1 to 2 cm in diameter within 4 to 7 days. Adjacent periodontal inflammation may be identified; however, pyogenic granuloma is unrelated to the regular forms of gingivitis and periodontitis. Pyogenic granulomas occur as exuberant granulation tissue responses after the removal of teeth, particularly the third molars. As such, the lesion emanates from the extraction sites, usually in response to an irritant that has fallen into the socket such as calculus, food, tooth fragments, or bone spicules. Pyogenic granulomas occur in other mucosal sites unrelated to the gingival sulcus, particularly on the tongue, lips, and buccal mucosa (Figure 9-57). In these locations it is assumed that biting of the tissue serves as the irritation that stimulates the hyperplastic response.

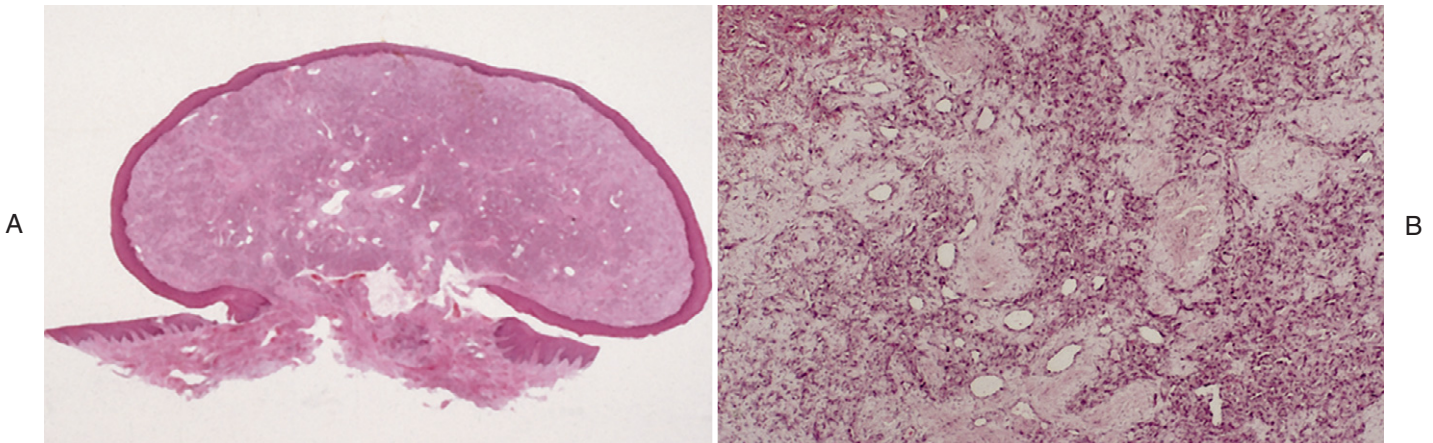
HISTOPATHOLOGY

Pyogenic granuloma is composed of granulation tissue, typified by a plethora of anastomosing endothelial-lined vascular channels engorged with erythrocytes and nodules of endothelial cells in medullary patterns (Figure 9-58). The endothelial cells are usually plump and vesicular, indicating active proliferation. Often the cells will have a pleomorphic character, and rarely, some of



FIGURE 9-57

Pyogenic granuloma. A purplish pedunculated nodular lesion of the commissure.

**FIGURE 9-58**

Pyogenic granuloma. **A**, Low-power microscopy demonstrating a raised lobular lesion with a thin stalk. **B**, Medium-power microscopy exhibiting a medullary pattern of endothelial cells intermingled with small vascular spaces and loose fibrous connective tissue. When ulcerated, lesions will also have acute and chronic inflammatory cells diffusely distributed throughout.

these actively proliferating hyperplasias closely resemble Kaposi sarcoma. Portions of the epithelium overlying the surface are usually ulcerated, leaving a fibrinous exudate with entrapped leukocytes. The loose connective tissue dispersed throughout the fibrovascular tissue and interposed between vascular channels is infiltrated predominantly by neutrophils and histiocytes.

TREATMENT

Although these are reactive hyperplasias, they have a relatively high rate of recurrence after simple excision. If the patient is pregnant, recurrence is common. Although many pyogenic granulomas are quite large, gingival lesions usually have a single stalk. After surgical excision the underlying tissue should be thoroughly curetted and root planing should be undertaken. Recurrence after surgery of pyogenic granulomas in extraggingival sites is uncommon.

HAMARTOMATOUS AND NEOPLASMS

Hemangioma

HEMANGIOMA: A proliferation of large (cavernous) or small (capillary) vascular channels occurring commonly in children; individual lesions have variable clinical courses.

Hemangiomas are relatively common benign proliferations of vascular channels that may be present at birth or arise during early childhood (Figure 9-59). Some slowly evolve, stabilize in size, and then either remain for life (hamartomatous) or slowly resolve to nor-

**FIGURE 9-59**

Hemangioma. Congenital hemangioma of the lower lip, exhibiting the usual bluish coloration and nodularity.

mal. Others may have a gradual but continuous growth pattern (benign).

Most are located within the skin, where they may be flat or raised. Flat (macular) hemangiomas can be relatively large, covering significant areas of the skin; these lesions are often referred to as *birthmarks*. Approximately 90% of such hemangiomas spontaneously involute by the time the patient has finished puberty. The remainder do not and are considered hamartomas. Vascular lesions of the lips and oral mucosa may arise in adulthood (Figure 9-60) and represent focal venous

dilatations that may become hyperplastic (Figure 9-61). This lesion is considered to be a reactive proliferation and is referred to as a *varix*.

CLINICAL FEATURES

Hemangiomas of the oral mucosa are usually raised, often multinodular, and distinctly reddish, blue, or purple. They most often occur in children and have no sex predilection. Compression with a glass microscopic slide against the lesion will usually cause blanching because the erythrocytes are compressed out of the vascular channels. Hemangiomas may arise in any mucosal

site but are most common in the tongue. Frequently, the multinodular character yields a racemose or polypoid appearance over the dorsal surface (Figure 9-62). These hemangiomas frequently extend deep into the intrinsic muscles of the tongue. Although many of these mucosal lesions will resolve once the patient has reached maturity, some remain constant, neither increasing in size nor undergoing involution.

Intramuscular hemangiomas may be encountered anywhere in the soft tissues of the head and neck. Within the oral cavity, they are usually seen on the tongue and lips. When they are deep seated, the surface tissue is often of normal coloration. Intramuscular hemangiomas cause a distortion of the area and have a spongy texture on palpation (Figure 9-63).

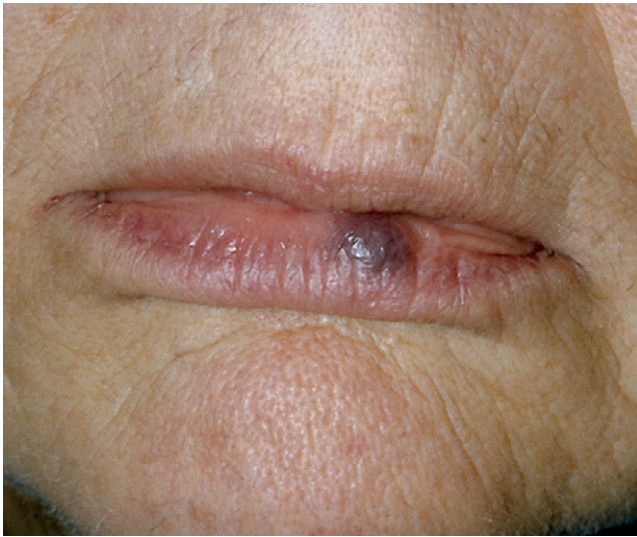


FIGURE 9-60

Varix. A lesion of the lower lip in an older adult is raised, soft, and bluish-purple in color.



FIGURE 9-62

Cavernous hemangioma. Large multilobular lesion of the dorsal and lateral tongue.

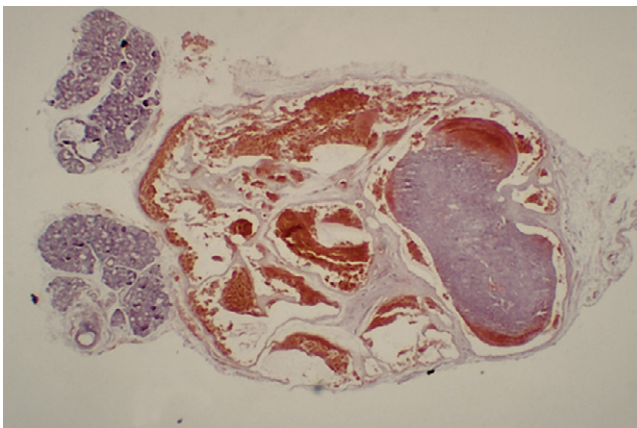


FIGURE 9-61

Varix. Low-power microscopy demonstrating a circumscribed collection of irregularly shaped, dilated venous structures with one vessel on the right side exhibiting thrombosis.



FIGURE 9-63

Intramuscular hemangioma. Lesion of the right upper lip exhibits swelling and some distortion; however, because the lesion is deep seated, the skin is normal in color.

A unique type of hemangioma, referred to as the *port-wine stain*, is sometimes encountered on the face. These are usually unilateral and appear to follow one, two, or all three of the divisions of the trigeminal nerve (Figure 9-64). Although there may be occasional nodular elevations, most port-wine stains are purplish, diffuse macules with irregular borders that are sharply demarcated from the normal skin.

A specific syndrome is sometimes identified with unilateral port-wine stains on the face when the individuals also have intracranial hemangiomas and epilepsy. This is termed *encephalotrigeminal angiomatosis*, also referred to as *Sturge-Weber syndrome*. The intracranial hemangiomas will often develop calcifications within the walls of the meningeal vessels, leading to a unique radiographic appearance of parallel radiopaque lines that have been termed *tramline* calcifications.

Arteriovenous **AV malformations** occur in the head and neck and may involve both soft and hard tissues. Central mandibular AV malformations are more common in females and are usually first detected during childhood. These rare lesions slowly expand the mandible and are painless. Auscultation with a stethoscope will frequently reveal a bruit. The bruit is accounted for by the flow of blood through the anomalous vascular pathways. Teeth overlying these vascular malformations are often compressible with a spongy sensation, and there may be a spontaneous hemorrhage around the gingival crevice. Aspiration with a large-bore needle will yield bright-red blood and frequently the syringe spontaneously fills without manipulation of the

plunger. This feature is indicative of the considerable arterial pressure that exists within AV malformations. The classic radiographic appearance of central AV malformation is that of a multilocular radiolucency. Importantly, the radiolucencies are quite small, appearing as worm holes in wood. Anatomically, the radiolucencies represent the tortuous course of the vascular channels through the bone. True *hemangiomas of bone* are also encountered. These vascular proliferations are under capillary or venous pressure and represent benign vascular proliferations identical to the ordinary hemangioma of the soft tissue. Central hemangiomas may also expand bone with a multilocular radiographic appearance; however, a bruit is not detected.

HISTOPATHOLOGY

Hemangiomas are composed of multiple, small capillary channels or large tortuous dilated vascular spaces densely packed with erythrocytes. The former are referred to as *capillary hemangiomas*, whereas the lesions with large channels are termed *cavernous hemangiomas*. Numerous closely compacted small endothelial-lined channels typify the capillary hemangioma (Figure 9-65). The endothelial cells are either spindle shaped or slightly elongated and plump. Although well-formed capillaries are present throughout, there may be foci of proliferating endothelial cells forming small aggregates that lack any attempt at lumen formation. A fibrous stroma is usually not prominent.

Capillary hemangiomas closely resemble pyogenic granulomas histologically. Unless irritated, inflammatory cells are not a usual component of hemangiomas, although inflammation is a typical finding in pyogenic



FIGURE 9-64
Port-wine stain capillary hemangioma. Congenital lesion following the distribution of the upper divisions of the trigeminal nerve on the right side of the face.

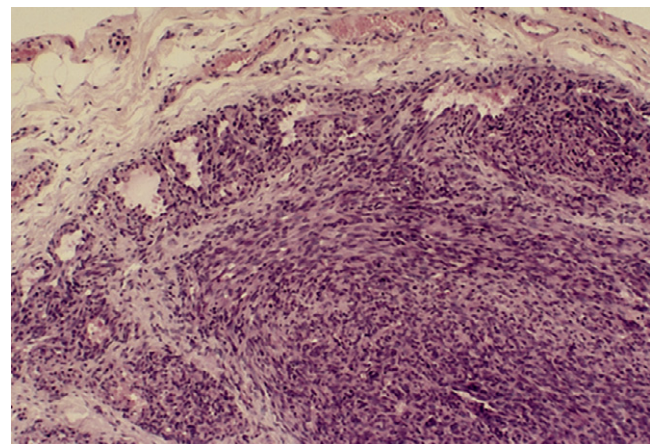


FIGURE 9-65
Capillary hemangioma. Low-power microscopy exhibiting a medullary pattern of a proliferation of endothelial cells forming numerous, small, densely packed capillaries with some larger vessels in the periphery.

granuloma. The cavernous hemangioma consists of large, irregularly shaped, dilated endothelial-lined channels that contain large aggregates of erythrocytes (Figure 9-66). The vascular channels are of variable calibers, usually separated by a mature fibrous stroma. As a rule, cavernous hemangiomas lack a muscular coat, although some of these vessels will occasionally show a smooth muscle circumferential media. The macular hemangiomas, such as port-wine stain, are composed of small caliber channels similar to capillary hemangioma; however, the vessels are usually separated from one another by a mature fibrous tissue stroma.

Central hemangiomas of the bone are usually of the cavernous type. The AV malformation is rarely subjected to biopsy, because surgical intervention can lead to profound hemorrhaging, which can result in death. These lesions are usually diagnosed with imaging studies such as Doppler angiography or contrast time-lapse angiography.

Histologically the AV malformation shows juxtaposed large vascular channels, most of which have either muscular or adventitial fibrous coats. These vascular channels replace the bone marrow, and the adjacent osseous trabeculae show evidence of osteoclastic resorption.

TREATMENT

Most hemangiomas in children are left untreated until puberty, anticipating spontaneous involution. Hemangiomas that persist into adult life usually become arrested in their growth potential and are often considered to represent hamartomas rather than true neoplasms. Lesions that appear to involve deeper structures are usually left untreated. In some cases for functional or cosmetic reasons, surgical excision may be attempted or sclerosing

agents may be used. Many mucocutaneous hemangiomas, particularly the port-wine stains, are responsive to laser therapy.

Within bone a central multilocular radiolucency that yields blood upon aspiration may represent a central AV malformation, central hemangioma, or aneurysmal bone cyst. The AV malformation contains blood under high pressure, and time-lapse angiography will disclose the high flow that is encountered in these lesions.

To prevent further destruction the treatment of choice is induced embolization administered through the feeder vessels. Frequently the malformation receives a bilateral vascular supply; mandibular lesions may even have feeder vessels derived from the vertebral arteries, further complicating attempts at treatment. Treatment is often essential, because spontaneous hemorrhage as the result of tooth loss could easily cause death.

Lymphangioma

LYMPHANGIOMA: A benign proliferation of lymphatic vessels that occurs as a focal superficial lesion within the oral cavity and as a massive diffuse lesion of the neck (cystic hygroma).

Lymphangiomas are excessive vascular proliferations of the lymphatic system. Like hemangiomas, most lymphatic vessel proliferations arise during childhood. No sex predilection exists. Two major types of lymphangiomas occur in the head and neck: (1) self-limiting tumors usually found in the oral mucosa and (2) **cystic hygroma** usually massive soft and fluctuant tumors and found in the lateral neck.

CLINICAL FEATURES

Oral mucosal lymphangiomas are usually encountered in the tongues of children (Figure 9-67), where they may spontaneously involute at puberty or reach a given size and persist without further growth. Clinically, they are often racemose, especially when they occur on the dorsal tongue. The grapelike clusters may have a yellowish appearance and are soft on palpation. The lips are the second most common site for intraoral lymphangioma. Cystic hygroma presents as a massive swelling of the lateral neck (Figure 9-68). These tumors are usually covered by normal-appearing skin and may be quite pendulous, being several centimeters in diameter. They usually arise during the first or second years of the patient's life; on palpation they have a decided cystic, fluctuant consistency. The proliferating lymphatic vessels frequently extend between muscle fibers and fascial planes, making their surgical removal problematic.

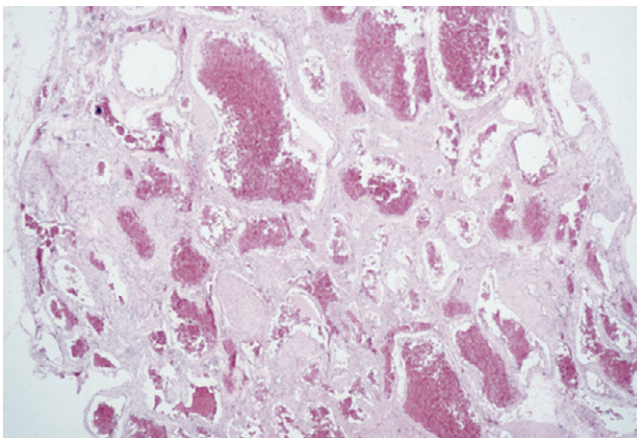


FIGURE 9-66

Cavernous hemangioma. Low-power microscopy demonstrating a circumscribed accumulation of large, irregularly shaped, thin-walled blood vessel engorged with red blood cells.

HISTOPATHOLOGY

The proliferating vessels of lymphangioma are thin walled and lined by plump endothelial cells. The lumens contain an eosinophilic proteinaceous coagulum with occasional erythrocytes and leukocytes. In lymphangioma of the tongue, the cavernous lymphatic channels usually extend between the rete ridges of the epithelium, producing papillomatous-like nodules on



FIGURE 9-67

Lymphangioma. Lesion involves the entire tongue and exhibits multiple small surface nodules resulting in macroglossia.



FIGURE 9-68

Cystic hygroma. The congenital, large, diffuse lymphangioma involves the deep structures of the neck of an infant.

the surface. The lymphatic channels about the epithelium without any intervening fibrous tissue (Figure 9-69). In cystic hygroma the histologic appearance is similar to lymphangioma of the oral submucosa. The channels are often quite large and of variable calibers, extend deep into the tissue, and traverse between muscle fibers and fibrous connective tissue (Figure 9-70). Although the lesion is infiltrative, it generally does not cause the destruction of neighboring structures.

TREATMENT

Lymphangiomas often spontaneously involute during puberty and are usually left untreated until the child reaches 18 years of age. Those that fail to involute usually

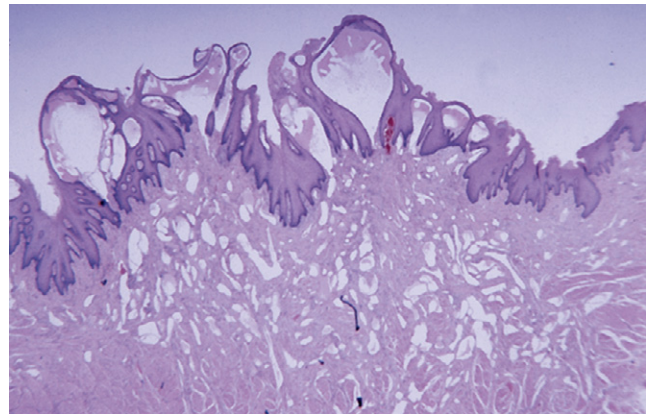


FIGURE 9-69

Lymphangioma. Low-power microscopy of a superficial mucosal lesion exhibiting the numerous clear vascular spaces throughout the submucosa and extending between the rete pegs, producing small, delicate surface nodules.

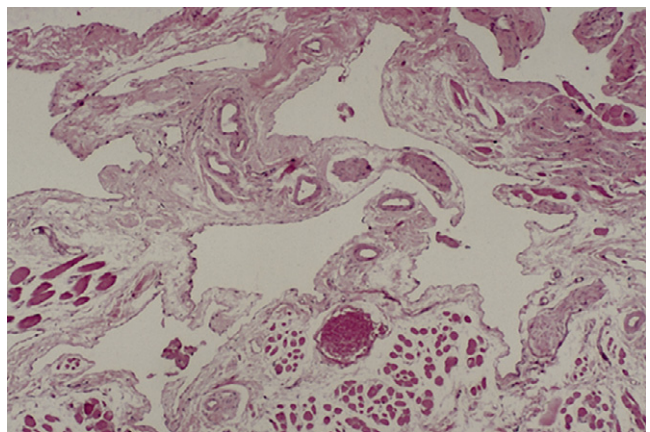


FIGURE 9-70

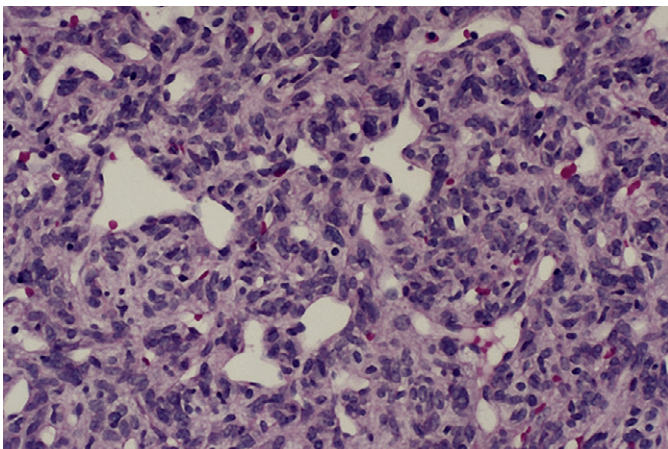
Lymphangioma. Low-power microscopy of large tortuous lymphatic spaces extending between the muscle bundles. Occasional vessels engorged with blood (*lower center*) are often found in these lesions.

demonstrate a cessation of growth and may be left untreated. Surgical excision is often deferred, because many of the tumors will recur as the result of inability to completely excise all of the vascular channels. Cryosurgery and laser surgery have been used with some success.

Angiosarcoma

ANGIOSARCOMA: A malignant, rare, rapidly growing lesion of endothelial cells that is more common in young patients and has a poor prognosis.

Malignant neoplasms of vascular endothelium are referred to as *angiosarcomas*. These tumors are extremely rare and may arise from the endothelial cells of either blood or lymphatic vessels. The **hemangioendothelioma** and **hemangiopericytoma** (Figure 9-71) are quasimalignant neoplasms of vascular endothelium and vascular pericytes, respectively. These neoplasms are extremely cellular and represent proliferations of the individual cells rather than blood channels per se, as encountered in hemangiomas. They are quite aggressive, tend to occur in children and young adults, and have a tendency for recurrence, although distant metastases are rare. The most commonly encountered angiosarcoma within the oral cavity is **Kaposi sarcoma**, which is associated with the human immunodeficiency virus (HIV) epidemic. These tumors are usually multiple, and whereas some are self-limiting in their growth potential, others are capable of becoming large. Angiosarcomas other than Kaposi sarcoma are rapidly growing tumors with aggressive behaviors and high propensities for hematogenous metastases. These tumors are extremely rare in the head and neck regions and only a few cases of tumors within the oral cavity have been reported.



Kaposi Sarcoma

KAPOSI SARCOMA: A unique form of angiosarcoma that occurs in elderly and HIV-positive patients and has a predilection for the palate.

Kaposi sarcoma (KS) that occurs in the absence of HIV infection is extremely rare. These tumors typically arise in the palate and lower extremities of elderly men. HIV-associated Kaposi sarcoma is commonly seen on the skin and within the oral cavity. The tumor is associated with a gamma herpesvirus, referred to as *KS-associated herpesvirus* or *human herpesvirus 8 (HHV-8)*. The homosexual risk group is most often involved, with very few cases occurring in intravenous (IV) drug users or female patients with HIV infection. When KS occurs in an HIV-infected patient, it usually carries the diagnosis of acquired immunodeficiency syndrome (AIDS).

CLINICAL FEATURES

On the skin, KS lesions evolve through a flat, macular plaque phase of purple discoloration that progresses into a nodular tumor configuration that is red, blue, or purple. The palate is the most common site for KS within the oral cavity, and both hard and soft palatal mucosae may be affected. As on the skin the early lesions are macular, red or blue, and well demarcated (Figure 9-72). These macular angiomatous proliferations frequently progress to large nodular tumefactions (Figure 9-73) that can become quite pendulous. They maintain their vascular pigmentation and are often associated with brown discoloration because of the deposition of hemosiderin pigment within the tumor mass. The facial gingiva is the second most common location for intraoral KS. Lesions usually fail to blanch on compression, because well-defined vascular channels are usually lacking.

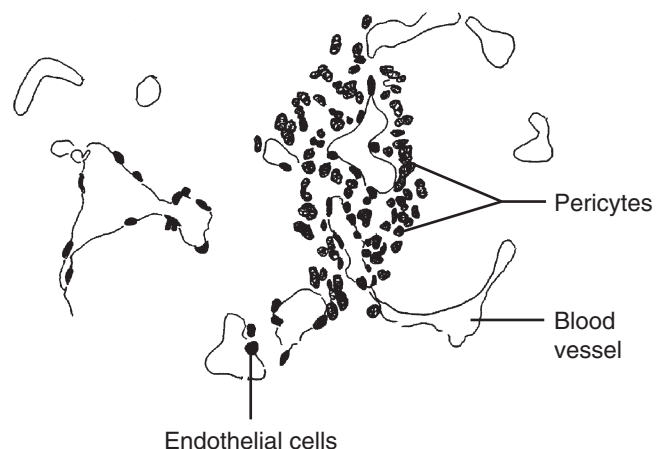
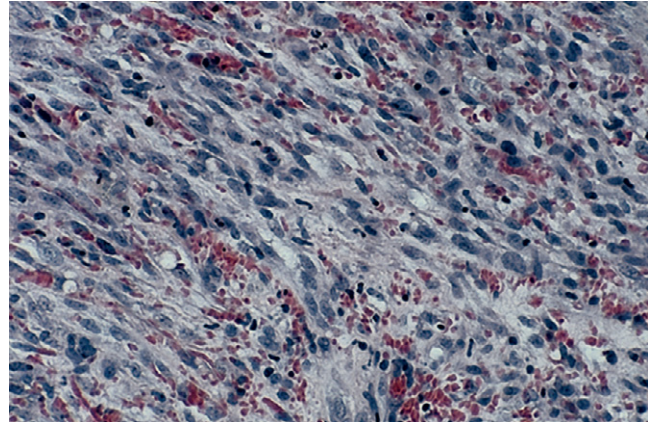


FIGURE 9-71

Hemangiopericytoma. Medium-power microscopy of cellular proliferation of the perivascular cells (pericytes), causing distortion of the endothelial-lined vascular spaces.

**FIGURE 9-72**

Kaposi sarcoma. Macular lesion on the palate of a human immunodeficiency syndrome (HIV)-positive patient.

**FIGURE 9-74**

Kaposi sarcoma. Medium-power microscopy, exhibiting the hyperchromatic and pleomorphic spindle endothelial cells found around partially formed vascular spaces against a background of extravasated red blood cells.

**FIGURE 9-73**

Kaposi sarcoma. Nodular form of a lesion on the palate of a human immunodeficiency syndrome (HIV)-positive patient.

HISTOPATHOLOGY

In the early plaque stage, numerous slitlike vascular channels are encountered, and the endothelial cells often assume a beaded configuration along the vascular lumens. The nodular lesions are hypercellular and composed of two cellular elements: (1) spindle cells with somewhat pleomorphic nuclei and (2) endothelial cells oriented around sinusoidal, slitlike vascular channels (Figure 9-74). Round capillary configurations may be admixed with the more sinusoidal-appearing cell population. Mitotic figures are not commonly seen, and cytologic atypia is usually evident yet relatively mild. Erythrocytes are encountered within the slitlike vascular channels, and many are extravasated. In addition, hemosiderin pigment granules are disbursed throughout the tumor.

TREATMENT

KS occurring in HIV-positive individuals is a multicentric disease. Patients often have multiple sites of involvement, and these multiple tumors represent a multicentric distribution rather than metastases from a primary tumor. Experimental research discloses that these tumor cells proliferate in response to various growth factors that are secreted in an autocrine or paracrine manner. A variety of treatments have been investigated, including local treatment and systemically administered growth factor inhibitors. Mucosal lesions less than 2 cm commonly resolve after injection with sclerosing agents or chemotherapeutic agents. Low-dose radiation therapy has also been shown to cause shrinkage of these vascular proliferations.

OSSEOUS AND CARTILAGINOUS TISSUE

Bone- and cartilage-forming tumors of the jaws are discussed in Chapter 4. Occasionally, osseous or cartilaginous tissue may develop within subcutaneous or submucosal connective tissue. Formation of normal-appearing cartilage and bone in soft tissue located away from the osteoprogenitor cells in bone is referred to as a *choristoma*. Choristomas are similar to hamartomas, because they tend to reach a given size and cease growing. Two reactive lesions are commonly derived from osteoprogenitor cellular elements of the gingiva: (1) peripheral ossifying fibroma, and (2) peripheral giant cell granuloma; they represent reactive hyperplasias with elaboration of bone and giant cells resembling osteoclasts, respectively. Another bone-forming reactive process that occurs within the substance of muscle is myositis ossificans. A true osteoma of

the soft tissue is probably nonexistent; nevertheless, compact bony nodules, referred to as *osteomas*, may be encountered in the soft tissue around the jaws and in the sinuses in **Gardner syndrome**. Some osteogenic sarcoma may arise from the periosteum of the jaws, giving the clinical appearance of a soft tissue mass.

DEVELOPMENTAL LESIONS

Soft Tissue Osteoma

SOFT TISSUE OSTEOMA: *A focal growth of normal-appearing bone developing within the connective tissue; commonly found in patients with Gardner syndrome.*

True osteomas of the soft tissue do not occur. As mentioned earlier, most of these represent choristomas. In Gardner syndrome, ossified structures with the appearance of mature, compact bone may arise within the soft tissue or adhere to the periosteum of the jaws. Supernumerary impacted teeth, facial bone osteomas, cutaneous nodules, and intestinal polyps that are premalignant characterize the syndrome. Other conditions in which calcified bodies occur within the soft tissue are calcinosis cutis and metastatic calcification, which may accompany hypercalcemia.

CLINICAL FEATURES

The so-called osteomas of Gardner syndrome may arise in the mandibular area. These calcified masses usually adhere to the periosteum and appear as nodules along the angle or inferior border of the mandible. On occasion, they may be intraosseous and prevent normal tooth eruption. They can be identified on panoramic radiographs as well-delineated or lobular spherical calcifications that usually measure 1 to 2 cm. These calcified bodies are also frequently identified within the paranasal sinuses; the frontal and maxillary sinuses are the more common locations. Dental radiographs will disclose the presence of from one to four supernumerary teeth, which are usually impacted. Multiple subcutaneous nodules of a fibrous nature representing fibrous hamartomas can be identified on the skin (usually located on the extremities). The most significant aspect of the syndrome involves the intestinal mucosa. Multiple polyps occur within the colon, and predictably, adenocarcinoma arises from these polyps.

HISTOPATHOLOGY

The osteomas have a similar microscopic appearance to osseous choristomas. Compact lamellar bone containing osteocyte nuclei within the lacunas is observed, and a fibrous or adipose marrow component can usually be identified, although most of these osseous bodies are dense with formation of haversian systems.

TREATMENT

It may be necessary to extract the supernumerary impacted teeth, because they may cause malocclusion of the remaining dentition. The osteomas can be excised if they are cosmetically or functionally problematic. Otherwise they are self-limiting in their growth and do not usually continue to enlarge during adult years. Many oncologists recommend prophylactic resection of the colon in the areas involved with polyps.

Osseous and Cartilaginous Choristoma

OSSEOUS AND CARTILAGINOUS CHORISTOMA:

A raised, firm, and movable soft tissue nodule containing a central nidus of bone, cartilage, or both, with self-limiting growth.

Osseous and cartilaginous choristomas are soft tissue masses in which normal-appearing bone and cartilage are found. They are benign and are self-limiting in their growth potential.

CLINICAL FEATURES

Osseous and cartilaginous choristomas occur most frequently in the tongue, with a predilection for the ventral surface of the submucosa. They are also seen in the floor of the mouth yet are quite rare in other mucosal locations. No sex predilection exists, and most of these lesions are initially detected in adults. On palpation they are extremely hard and may be mistaken for a sialolith within a minor salivary gland. While indurated, they are usually easily movable. Another lesion of putative cartilaginous origin is the **ectomesenchymal chondromyxoid tumor**. This benign tumor is found in the anterior aspect of the tongue and appears as a soft-to-firm, well-demarcated submucosal mass.

HISTOPATHOLOGY

Osseous and cartilaginous choristomas are characterized by the formation of mature bone, cartilage, or both. Mature osseous trabeculae contain lacunae with osteocytes. The trabeculae may resemble endosteum or may be more compact with the appearance of cortical bone. In such cases, haversian systems can be identified. The intervening connective tissue resembles normal bone marrow, being either fibrous or adipose. Hematogenous marrow is rarely identified in osseous choristomas. In cartilaginous choristoma, hyaline cartilage can be identified, showing its usual basophilic hyalinized appearance. Lacunae contain chondrocyte nuclei, which are small, pyknotic, and monomorphic. The periphery is usually round, smooth, and enveloped by mature fibrous connective tissue. Some of these choristomas demonstrate endochondral bone formation.

The ectomesenchymal chondromyxoid tumor does not contain mature cartilage; rather, a well-demarcated mass of mesenchymal cells displaces adjacent muscle fibers without showing significant infiltration of contiguous tissues. The cells are polygonal to spindle in shape, with a myxomatous loose cell growth pattern. This uncommon neoplasm shows differentiation markers for both ectodermal (epithelial) and mesenchymal tissues. The tumor cells are positive for both cytokeratins and vimentin; they also stain for S-100 protein.

TREATMENT

Enucleation is the treatment of choice for osteocartilagenous choristomas and ectomesenchymal chondromyxoid tumors; recurrence is rare.

REACTIVE LESION

Myositis Ossificans

MYOSITIS OSSIFICANS: A rare reaction to injury of a muscle consisting of fibrosis and an associated deposition of bone, resulting in pain, swelling, and limitation of motion.

In the maxillofacial complex, myositis ossificans is most often encountered in the masseter or pterygoid muscles. A history of blunt trauma can sometimes be obtained. These reactive lesions tend to be self-limiting yet may cause dysfunction of the affected muscle.

CLINICAL FEATURES

Myositis ossificans is a rare reactive lesion of muscle characterized by fibroblastic proliferation and elaboration of osseous trabeculae. The affected muscle has limitation of motion, is usually swollen, and may be tender on palpation. When palpated, the mass is considerably indurated. In the masseter and pterygoid muscles, limited jaw opening may be observed. Radiographs will disclose multiple foci of ossification within the substance of the musculature. Computed tomography (CT) scans with a bone window are ideal for demonstrating these lesions. The ossification is usually dense and appears as a radiopacity on routine radiographs.

HISTOPATHOLOGY

Within the substance of skeletal muscle is a diffuse proliferation of fibroblastic spindle cells with an elaboration of either delicate or thin collagen fibers. The lesion is not well demarcated and may appear to infiltrate between contiguous skeletal muscle fibers. In the central area, osteogenesis is identifiable with an elaboration of delicate osseous trabeculae undergoing various stages of calcification. Older lesions may show more compact bone. This osseous tissue is mature and benign.

TREATMENT

Once myositis ossificans has been diagnosed, surgical intervention is usually deferred. Removal of the involved muscle does not provide any improvement and might worsen function. Alternatively, if the mandible is completely restricted in motion, it may be advisable to debulk the involved area.

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10 *Salivary Gland Disorders*

CHAPTER OUTLINE

REACTIVE LESIONS

Mucocele
Mucus Retention Cyst
Sialolithiasis
Chronic Sclerosing Sialadenitis
Necrotizing Sialometaplasia

INFECTIONS

Acute Parotitis
Viral Endemic Parotitis (Mumps)
Bacterial Sialadenitis

IMMUNE-MEDIATED DISEASES

Lymphoepithelial Sialadenitis
Sjögren Syndrome

SALIVARY GLAND TUMORS

BENIGN SALIVARY GLAND TUMORS

Pleomorphic Adenoma
Monomorphic Adenoma
Papillary Cystadenoma Lymphomatosum
Oncocytoma
Other Adenomas

MALIGNANT SALIVARY GLAND TUMORS

Mucoepidermoid Carcinoma
Adenoid Cystic Carcinoma
Acinic Cell Carcinoma
Polymorphous Low-Grade
Adenocarcinoma
Other Adenocarcinomas

ADDITIONAL KEY TERMS

Adenocarcinomas
Adenomas
Basal cell adenocarcinoma
Basal cell adenoma
Canalicular adenoma
Chronic sclerosing sialadenitis
Clear cell oncocytoma
Cystadenoma
Intraductal papilloma
Inverted ductal papilloma
Mixed tumor
Oncocytic cyst
Ranula
Salivary duct carcinoma
Sebaceous adenoma
Sialadenoma papilliferum



The diseases that occur in the major and minor salivary glands of the orofacial structures are also encountered in the submucosal glands of all the upper air passages, including the mucus-secreting glands of the nose, paranasal sinuses, and larynx. The basic disease processes that affect the seromucous glands are reactive and obstructive lesions, infections, immunopathologic disorders, and neoplasms. A common feature of all of these processes is swelling of the gland. Pain is a common accompanying symptom in infectious and obstructive lesions, whereas immunologic and neoplastic disorders are usually characterized by painless enlargement.

Because most salivary gland diseases affect the ductal and secretory components and most neoplastic diseases arise from various cell types of the glandular tree, it is helpful in the understanding of these pathologic processes to be familiar with the normal histology of these glands (Figure 10-1).

Salivary glands, whether major or minor, arise embryologically from the primitive ectoderm of the stomatodeum. The gland primordia penetrate the submucosa as tubular invaginations that ultimately differentiate into end bulbs with secretory capabilities. A mature gland may contain three types of acinar (secretory) cells: (1) mucous, (2) seromucous, and (3) serous. In some glands, mucous acini are capped by serous or seromucous demilunes. Contractile myoepithelial cells that are surrounded by a basement membrane envelop the acinar cells. The secretory fluids and proteins enter the small cuboidal-lined terminal or intercalated ducts and progress to the mitochondrial-rich striated ducts. These two ductal elements residing within the salivary gland proper are components of the intralobular ducts. Numerous acinar clusters secrete their products into these ducts that collectively drain into much larger ducts composed of basilar reserve cells, stratified epithelium, and lumenally oriented cuboidal or columnar cells. These larger ducts exit the lobule as extralobular ducts that eventually converge into the major salivary ducts. As these ducts reach the surface, they are lined by stratified squamous epithelium, although some still have lumenally oriented cuboidal cells. Most tumors of the salivary glands are classified according to the histologic components they resemble.

Three major glands (parotid, submandibular, and sublingual) and numerous mucosal minor salivary glands secrete into the oral cavity. The minor glands are distributed throughout the oral cavity, with the exception of the dorsal tongue and attached gingiva. It is estimated that on the average, 450 minor glands can be found in the hard palate, 220 in the soft palate, and 8 in the uvula. It is important to realize that the posterolateral aspect of the hard palate is the most common location for salivary neoplasms within the oral cavity.

Deficient secretion occurs when the ductal drainage system is severed or blocked. Additionally, xerostomia may evolve as a consequence of acinar damage from infectious, immune, or sclerotic changes that occur secondary to obstructive disease. Salivary swellings are seen when the glands become infiltrated by leukocytes as occurs in obstruction or immunopathologic disease, edema associated with infection, fatty infiltration, or neoplastic processes.

Because the parotid gland overlies the facial (VII) nerve, tumors arising in this site may cause nerve paresis with attending facial weakness. This is an ominous sign, because it may be the harbinger of a malignant parotid tumor that has invaded the nerve.

Clinical examination has been demonstrated to be valuable when attempting to reveal the basic nature of a salivary disease process. Palpation of swellings of the

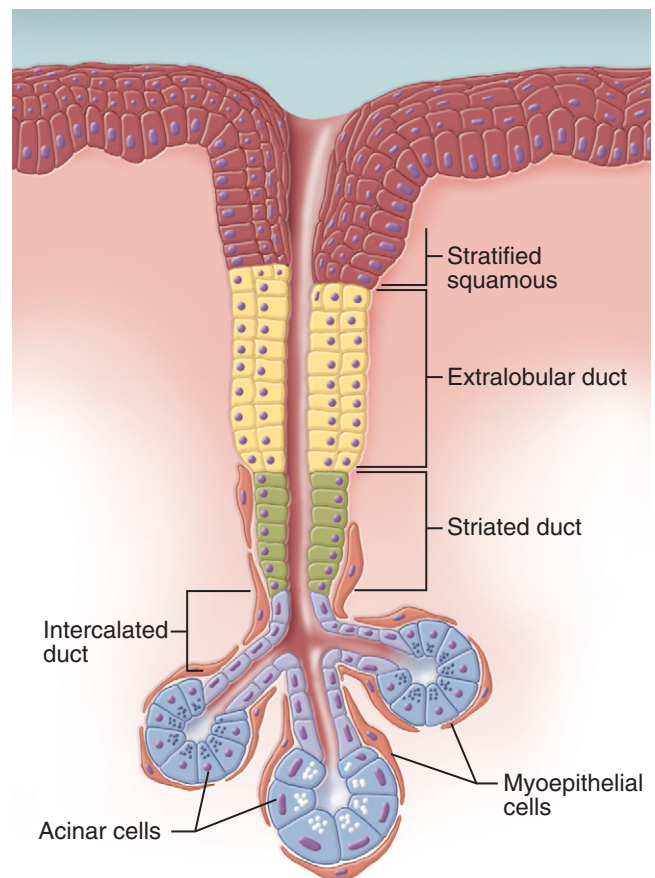


FIGURE 10-1
Components of the adult salivary gland secretory unit.

Acinar secretions move from the intercalated ducts to the larger striated duct, both lined by cuboidal epithelium. The saliva is further transported, with help from contractile myoepithelial cells, into the stratified, columnar, extralobular ducts, ultimately emerging from the mucosa through the excretory duct lined by stratified squamous epithelium.

major glands or of the oral mucosa containing minor glands is diagnostically useful, because soft or fluctuant swellings are the usual features of benign processes, whereas fixed and indurated swellings are more indicative of malignancy.

REACTIVE LESIONS

Salivary glands react to injury or obstruction by undergoing atrophic degeneration and necrosis with replacement of the parenchyma by inflammatory cells and, ultimately, fibrous scarring. Certainly bacterial or viral infections of the gland or immunologic reactions to autoantigens may culminate in the same processes of degeneration, necrosis, and fibrosis. Those diseases that are considered to be reactive in nature are noninfectious; they represent responses to direct trauma or obstruction to the flow of saliva. A few are of unknown origin.

Obstruction to flow may occur as a consequence of duct blockage by an object in the ductal lumen, stricture

of a duct with narrowing of the lumen, or severance of a duct with pooling of mucin within the tissue. In all three instances, salivary obstruction evolves; as glandular secretions accumulate within the ductal lumina, back pressure changes evolve and lead to acinar atrophic degeneration. As acinar cells progressively degenerate subsequent to obstruction, apoptosis and necrosis ensue. These degenerative changes are subtle, evolving over weeks or months, and are such that histologic evidence of frank necrosis is generally absent. The degenerating secretory units disappear; and as cells die, a mild chronic inflammatory cell infiltrate composed of lymphocytes and plasma cells appear. Once acini are no longer evident, the parenchyma undergoes a progressive fibrosis (sclerosis), a process common to all reactive lesions. In the salivary glands it is referred to as **chronic sclerosing sialadenitis** (Box 10-1). It is notable that the ductal system is more resistant to the obstructive process than the acini. When tissue from chronic sclerosing sialadenitis is viewed microscopically, the ductal elements are often seen to remain, whereas the acini are completely degenerated (Figure 10-2). The remaining ducts have little ability to generate secretion products, resulting in a greatly reduced outward flow. This stasis predisposes the development of retrograde bacterial infections.

BOX 10-1

Common Causes of Chronic Sclerosing Sialadenitis

- Excretory obstructions
- Infections
- Radiation
- Autoimmune diseases
- Systemic and metabolic conditions
- Medications and drugs

MUCOCELE

MUCOCELE: Tissue swelling composed of pooled mucus that escaped into the connective tissue from a severed excretory duct.

When a salivary duct is severed, the acinar cells will continue to secrete saliva into the severed duct. At the

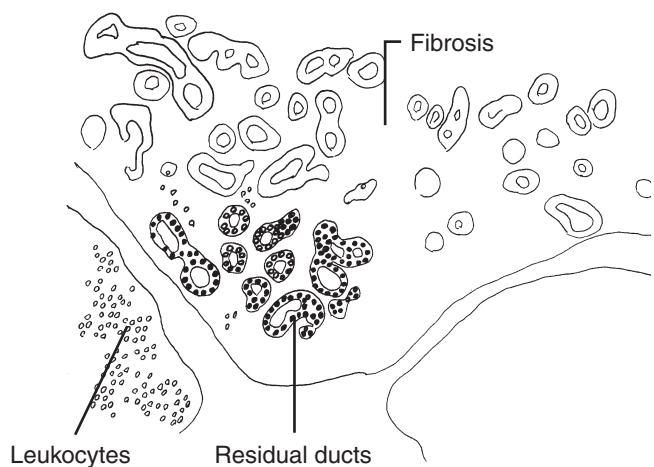
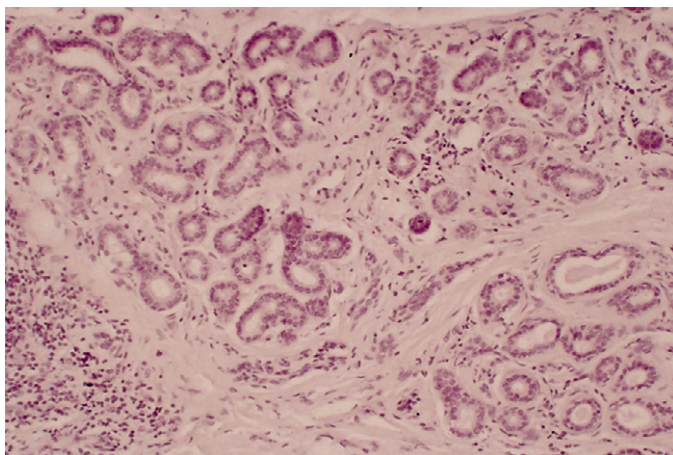


FIGURE 10-2

Chronic sclerosing sialadenitis. The intralobular ducts remain intact and dilated. The acini have degenerated and are replaced by leukocyte infiltration and fibrosis of the salivary lobule.

site of severance the secretory products escape into the connective tissue forming a pool of mucus that distends the surrounding tissue (Figure 10-3). This mucous escape (extravasation) phenomenon is commonly termed a *mucocoele*. The minor salivary glands of the lower lip are most prone to severance as a consequence of injury or biting of the mucosa, although other intraoral or even laryngeal minor mucous glands can be affected. Mucocoeles of the major salivary glands are quite rare. Occasionally, such mucous extravasation reactions will occur in the floor of the mouth as a consequence of minor sublingual gland duct severance. These mucocoeles have the finely vascularized, distended appearance of a frog's belly and are referred to as **ranulas**. When the major submandibular duct (Wharton duct) is punctured or severed, massive mucous extravasation may occur deeply within the submental, submandibular, or sublingual region. Mucous extravasation of this nature is termed *plunging mucocoele* or *ranula*. Plunging mucocoeles are of concern, because they are capable of causing a severe compromise of the airway.

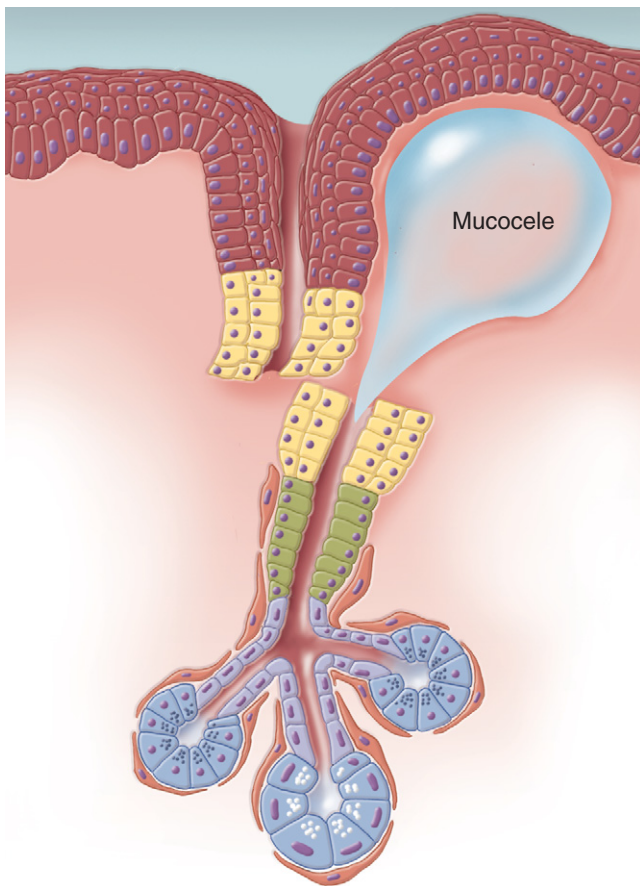


FIGURE 10-3

Mucocoele. Mucus escapes from a severed duct and accumulates within the submucosal connective tissue.

Although mucocoeles do not cause direct obstruction to the flow of saliva, the amount of secretions that can be extravasated is limited by the distensibility of the surrounding tissue. Although mucocoeles can become large, most are of limited size. As they enlarge, the gland that supplies mucin through the severed duct (the *feeder gland*) becomes compressed; eventually obstructive changes develop.

On occasion, radiographs of the maxillary sinuses will reveal focal nodular hyperplastic enlargements of the maxillary sinus lining mucosa. They are sometimes referred to as *antral mucocoeles*, when in fact such lesions represent inflammatory polyps.

Some neoplastic lesions may clinically resemble mucocoeles, most notably mucoepidermoid carcinoma. This fact alone dictates that all suspected mucocoeles should be submitted for microscopic examination. Others have an appearance similar to a cavernous hemangioma. When mucocoeles are superficial, they may clinically and histologically resemble blisters seen in some bullous and desquamative diseases; however, the latter are usually multifocal.

CLINICAL FEATURES

Mucocoeles are most often encountered in children and young adults, although they may occur at any age. Almost two thirds of all mucocoeles occur during the first three decades of life. Both males and females are equally affected. The mucosal surface of the lower lip is the favored site (Figure 10-4), followed by the buccal mucosa, the floor of the mouth, ventral tongue, and palate. Mucocoeles of the upper lip are uncommon. It



FIGURE 10-4

Mucocoele of the left lower lip. Lesion is soft and fluctuant on palpation.

should be recalled that minor salivary glands are ubiquitous within the oral cavity, with the exception of the anterior dorsal tongue and facial attached gingiva. Therefore mucocèles can arise in any oral location that harbors minor salivary tissue.

The clinical appearance of a mucocèle is dependent on its location within the submucosa. More superficial zones of mucous extravasation present a fluctuant mass with a bluish translucent appearance. In some mucocèles the trauma that initiated the ductal severance or the continued trauma by the dentition may result in hemorrhage. When the extravasated mucin is admixed with erythrocytes, an ecchymotic mucocèle develops and may appear deep blue or reddish purple, resembling a cavernous hemangioma. More deep-seated accumulations may simply present as a soft or fluctuant submucosal nodule of normal mucosal coloration. The patient usually has a history of injury to the area, followed by progressive swelling over a 2- to 4-day period.

Commonly, patients will describe a fluctuation in size; however, after the initial traumatic episode, pain is seldom a complaint. The amount of the fluctuation may be barely noticeable or significant to the point that the lesion disappears only to recur to its original size within a few days. Under these circumstances the patient will probably reinjure the area, allowing the mucin to escape through the thinned mucosal epithelium.

After the small puncture heals, the secretions reaccumulate, resulting in the recurrence. Initially, mucocèles are well circumscribed. With repeated trauma they may become nodular, more diffuse, and firmer on palpation. In the floor of the mouth, ranulas are generally located laterally and tend to be quite translucent with surface vascular markings readily apparent (Figure 10-5).



FIGURE 10-5

Ranula. Patient exhibits a fluctuant mucous escape phenomenon located off the midline in the floor of the mouth.

The plunging ranula is deep seated and is the result of extravasation into the submandibular or submental space. These lesions are soft on palpation, fluctuant, and often clinically evident as submental or submandibular swellings. Extension deep into the neck to involve the hyoid region can compromise the airway.

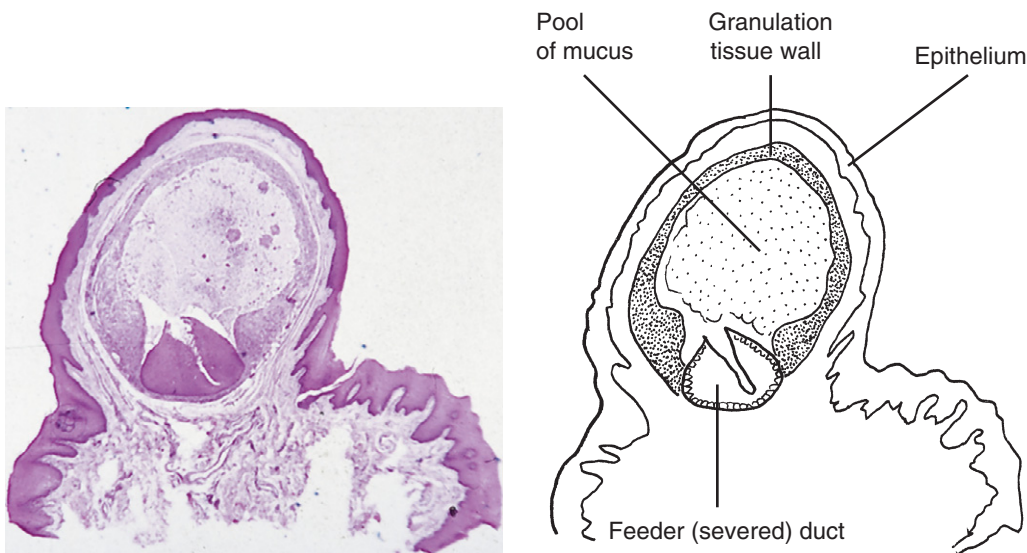
HISTOPATHOLOGY

An underlying pool of mucin distends the surface epithelium. This mucin is generally walled off by a rim of either granulation tissue or, in long-standing lesions, by condensed collagen that gives an encapsulated appearance. An epithelial lining is lacking (Figure 10-6). The mucinous material is basophilic or amphophilic and contains neutrophils and large, round-to-oval, foam cell histiocytes. These same cells infiltrate the granulation tissue wall. Occasionally, the base of the mucocèle on a fortuitous tissue section will reveal the presence of the feeder duct. The underlying salivary lobules that supply secretions through the feeder duct show varying degrees of chronic sclerosing sialadenitis, depending on the duration of the process. Long-standing mucocèles will show extensive acinar degeneration with fibrosis and minimal inflammation, whereas more recently traumatized lesions will show mononuclear infiltration with very little fibrosis.

Mucocèles that have been present for many weeks or those that are repeatedly traumatized to allow mucous escape often show histologic evidence of organization, an attempt at healing. Budding vascular channels and granulation tissue, lacking the unilocular encapsulated appearance of the uncomplicated mucocèle, will infiltrate the zone of mucous extravasation. Likewise, plunging mucocèles are characterized by diffuse foci of mucin admixed with granulation tissue, neutrophils, and foamy histiocytes. This mucous extravasation often extends between salivary lobules and along fascial and muscle planes.

TREATMENT

The typical minor gland mucocèle will not resolve of its own accord and must be surgically excised. To minimize the chance for recurrence, the underlying feeder glands should be removed in continuity with the mucocèle or extirpated from the base of the surgical bed after the removal of the lesion. Postsurgical transient paresthesia sometimes occurs when branches of the mental nerve are severed. Oral floor ranulas can also be excised; however, derroofing or *marsupialization* has been advocated as an alternative procedure. The rationale for marsupialization is predicated on the presence of an epithelial-lined cavity of mucous retention. Because most ranulas are mucocèles that lack an epithelial lining, marsupialization is to be discouraged. Plunging ranulas should be attended to quickly, because airway obstruction may

**FIGURE 10-6**

Mucocele. Microscopic appearance showing pooled mucin, a granulation tissue wall, distended overlying epithelium, and remnants of the severed feeder duct.

ensue. The mucinous material should be removed by aspiration, surgery, or both to relieve airway compression, followed by cannulation and repair of the major duct when possible.

MUCUS RETENTION CYST

MUCUS RETENTION CYST: *Swelling caused by an obstruction of a salivary gland excretory duct resulting in an epithelial-lined cavity containing mucus.*

True mucus retention cysts, sometimes referred to as *true mucoceles* or *sialocysts*, are aneurysm-like dilatations of salivary ducts containing mucus. Alternatively, some of these lesions may represent true blind cysts that are not in continuity with the ductal system (Figure 10-7). Unlike a mucocele that is surrounded by granulation tissue, the mucus retention cyst is lined by epithelium. These cysts rarely involve the major salivary glands; when they do, they can be multiple (dysgenic or polycystic disease of the parotid gland) (Figure 10-8). More often, mucus retention cysts arise in the oral minor salivary glands, where they are solitary but may be either unilocular or multilocular lesions. Clinically a mucus retention cyst is indistinguishable from a mucocele and may resemble low-grade mucoepidermoid carcinoma.

CLINICAL FEATURES

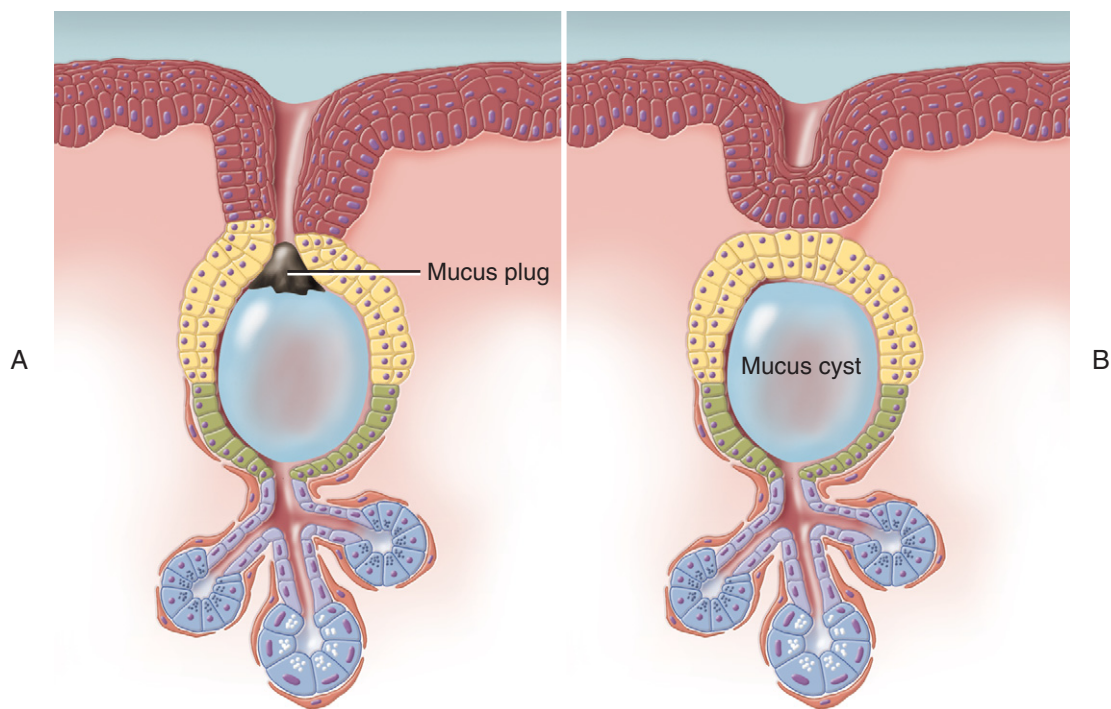
True mucus retention cysts are more often encountered among adults throughout the third to eighth decades, although they may occur at any age. Those cysts located

in the major salivary glands show a marked predilection for the parotid gland, which accounts for almost 90% of cysts of the major glands. When cysts occur in this location, the mean age of patients is 45 years. Parotid cysts are usually located in the superficial lobe and present as fluctuant, well-defined masses anterior to the ear or overlying the angle of the mandible. A history of slow progressive enlargement is usually noted. Within the oral cavity the floor of the mouth is the most common site, followed by the buccal mucosa and the lower lip. The lesions are painless, cystic, fluctuant, and generally superficial. In these instances they have a translucent, bluish appearance.

Deep-seated cysts may be detectable only during bimanual palpation. A specific histologic type of cyst that involves the minor salivary glands is the **oncocytic cyst**, which is most frequently seen in the buccal mucosa and lips in older patients (mean age: 60 years). Oncocytic cysts are usually identified as painless, sessile, dome-shaped masses of normal coloration that are located just below the surface in the buccal mucosa, vestibule, and lips. This type of cyst often has a history of fluctuation in size.

HISTOPATHOLOGY

The surface stratified squamous mucosal epithelium of the oral cavity is distended by a cystic cavity that is lined by cuboidal or, occasionally, columnar ductlike epithelium (Figure 10-9, A). The cytoplasm of these ductal lining cells is either eosinophilic or clear, and some may show evidence of mucous differentiation. Although

**FIGURE 10-7**

Mucus retention cyst. **A**, Some are hypothesized to arise as ductal dilatations from obstruction by mucous plugs. **B**, Other salivary mucous cysts are thought to occur as isolated blind cysts.

**FIGURE 10-8**

Dysgenic polycystic disease. **A**, Clinical appearance of a fluctuant parotid mass located beneath the earlobe and distal to the angle of the mandible. **B**, Injected opaque dye defines the cyst as a rounded radiopacity (*lower right*).

70% of these cysts are unilocular, 30% of them show multilocular patterns, sometimes with small papillary projections into the cystic lumens (Figure 10-9, B). The surrounding fibrous tissue may be compressed yet is rarely inflamed. The underlying gland lobules sometimes show evidence of chronic sclerosing sialadenitis. Those cysts arising in the parotid gland usually have a well-defined fibrous capsule that separates the cyst from the parotid parenchyma. Whether the mucus retention cyst is a true cyst of salivary duct origin or a focal dilatation caused by obstruction is not always clear. Indeed, the two processes are not mutually exclusive. Nevertheless, although the cyst cavity may contain congealed mucin, there may not be evidence of a stone or another readily identifiable source of obstruction that might result in a focal, aneurysmal, ductal dilatation. The oncocytic cyst, which favors older individuals, shows a distinctive, histologic appearance. The lining cells are columnar and often pseudostratified, and their cytoplasm is strikingly eosinophilic, typical of oncocytes. The lumen is filled

with eosinophilic, proteinaceous material thought to represent inspissated mucin. The adjacent gland lobules show evidence of obstructive chronic sclerosing sialadenitis. Oncocytic changes are often seen in the ducts of the adjacent glands. Rare varieties of mucus retention cysts occur that are multilobular with papillary projections and may be confused with cystadenomas.

TREATMENT

Simple excision is the treatment of choice. Care must be taken to avoid rupturing the delicate cystic sac at the time of surgery. Recurrence is rare; however, damage to adjacent glands may result in the formation of a mucocele.

SIALOLITHIASIS

SIALOLITHIASIS: *The presence of one or more oval or round calcified structures (salivary stones) in a duct of a major or minor salivary gland.*

Salivary stones can form within the lumens of major and minor salivary glands. In the major salivary glands the submandibular gland is most commonly involved; the consequences of duct blockage in the major salivary glands are more significant than when stones form in oral mucosal minor salivary gland ducts. In the major salivary glands prolonged blockage can lead to complete degeneration of parenchyma with secretory shutdown. During the process of obstruction, salivary retention with ductal dilatation results in pain and swelling. Glands that are no longer functional become subject to retrograde bacterial infections that can cause severe pain.

Stones that develop in other ductal systems of the body, such as uroliths (kidney stones) and choleliths (gall stones), have unique mineral contents and are associated with specific underlying predisposing conditions. Cholelithiasis is associated with bile secretion changes, infection, and stasis in the biliary tree. Gall stones are composed of either cholesterol or bilirubin. Kidney stones are usually calcium containing and develop as a consequence of hypercalciuria with or without hypercalcemia. Conversely, salivary stones are not associated with hypercalcemia; no specific secretory predisposing condition has been identified in sialolithiasis. For unknown reasons it is assumed that congealed mucin, protein, and desquamated ductal epithelial cells form a small nidus on which calcium salts precipitate (Figure 10-10). The small nidus then allows concentric lamellar crystallizations to occur; the sialolith increases in diameter as layer after layer of salts becomes deposited, much like growth rings in a tree. Microliths would probably be expelled easily into the saliva. Those that are not expelled usually continue to enlarge until a duct branch or even the major duct becomes occluded.

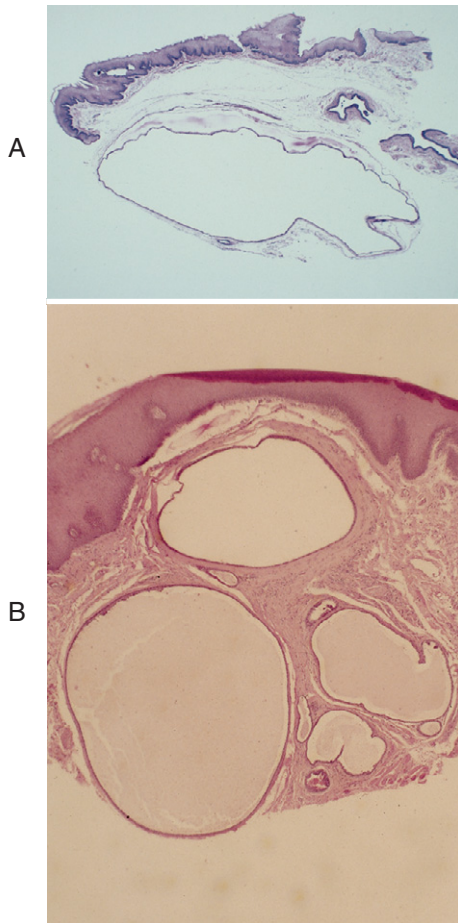


FIGURE 10-9
Mucus retention cyst. Lesions are located in the submucosa.
A, Unilocular. **B,** Multilocular.

CLINICAL FEATURES

About 80% of all sialoliths affect the major salivary glands; 75% of these have a predilection for the more viscous-secreting submandibular gland. The parotid gland is involved in 20% of the cases, with only 5% involvement of the sublingual gland (Table 10-1). Rare bilateral cases have been observed. Although the main duct is usually the site of the stone, multiple sialoliths can develop within ductal branches throughout the gland, and long-standing lesions may result in complete calcification of the entire gland. Stones are rare in children. The average age of patients with sialolith formation is 45, and no sex preference exists. Although some stones

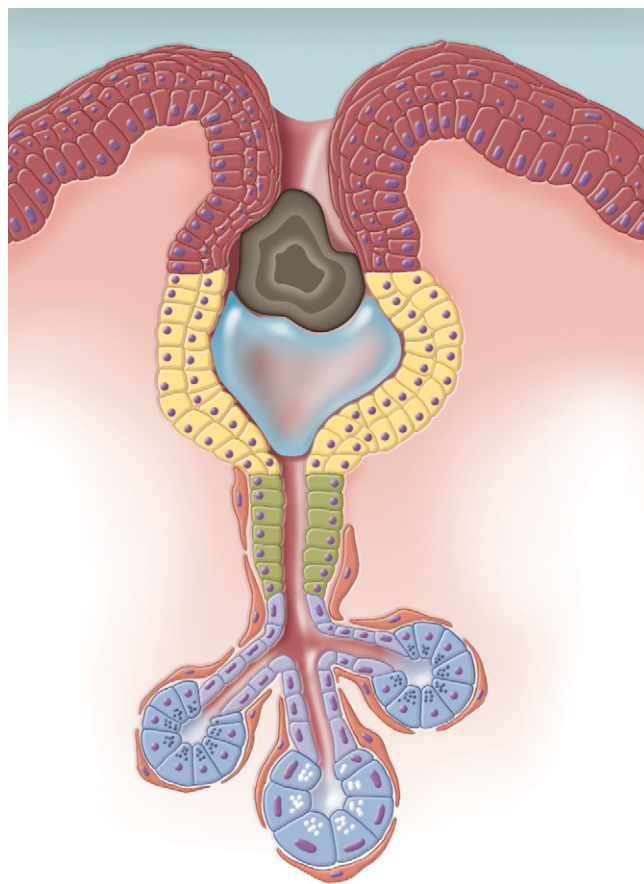


FIGURE 10-10
Sialolithiasis. Sialolith obstructs the flow of mucin, resulting in ductal distension.

are asymptomatic and are detected on dental radiographs taken for other purposes, most will cause symptoms.

The chief complaints are pain and swelling. Swelling is the consequence of ductal dilatation caused by retention of mucin in the blocked ducts. The swelling is most often observed at mealtimes or on direct stimulation of saliva production with a lemon drop candy. A persistent swelling eventually evolves in patients with chronic obstruction as the enlargement becomes a chronic sialadenitis containing inflammatory cells and interstitial edema. The pain is described as a pulling, drawing, or stinging sensation that can be quite uncomfortable if the entire duct is blocked. Partial obstruction occurs when pressure increases but saliva can escape around the stone or when only a branch rather than the main duct is blocked. In these situations the symptoms are mild or transient.

When a submandibular gland becomes symptomatic, unilateral glandular enlargement can be seen medial to the inferior border of the mandible. On palpation the swelling is firm yet tender (Figure 10-11, A). An occlusal radiograph will typically disclose the presence of a calcification in the floor of the mouth along the course of the major duct (Figure 10-11, B). If only branches of the duct at the level of the submandibular gland are affected, a posterior occlusal film, submental vertex, or lateral jaw film may be required to disclose the stone. Panoramic radiographs are also used to demonstrate submandibular duct stones; however, they are often projected over the image of the mandible, masquerading as intrabony opacities. Parotid stones, which usually cause firm swellings over the ramus of the mandible, can usually be visualized on a panoramic film. When radiographs fail to disclose the presence of calcified bodies in a gland, ultrasound imaging, orsialography may be indicated. Not all sialoliths are sufficiently calcified to become radiographically demonstrable.

The recoverability and regenerative capacity of an obstructed gland depends on the degree of acinar necrosis and lobular fibrosis. When the secretory capacity is destroyed and normal secretions cannot flush the ducts, a retrograde infection can ensue. In these instances pyogenic infections can result in persistent swelling with acute persistent pain, fever, and malaise. Often the affected gland and distended ducts become filled with purulent exudate.

Minor salivary gland sialolithiasis is most often seen in the upper lip and buccal mucosa. Because minor

Table 10-1 Incidence of Sialolithiasis in Major and Minor Salivary Glands

Major Glands	Incidence	Minor Glands	Incidence
Submandibular gland	73%	Lips	37%
Parotid gland	23%	Buccal mucosa	34%
Sublingual gland	4%	Floor of the mouth	9%
		All other sites	20%

salivary glands are small, a transient enlargement is not seen during meals. Rather, the stone itself is often clinically obvious or is readily palpable as a hard, movable nodule within the submucosa.

HISTOPATHOLOGY

On gross examination most sialoliths are yellowish-white, round to oval, and heavily calcified. Some are multinodular, whereas others are found in aggregates. After decalcification the stones exhibit lamination with concentric rings of basophilic bands. The material is otherwise acellular and amorphous. The outer margin

may contain aggregates of microbial colonies. When the glandular elements are submitted for microscopic examination, the ductal lining that surrounds the sialolith shows a variety of reactive changes. These include squamous and mucous cell metaplasia whereby the duct lining thickens into a stratified squamous epithelium that contains numerous mucous goblet cells. Occasionally the columnar cells show true cilia. The periductal connective tissue is often densely infiltrated by lymphocytes and plasma cells (Figure 10-12). The rest of the gland will usually show varying progressive consequences of obstruction. In early disease the acini

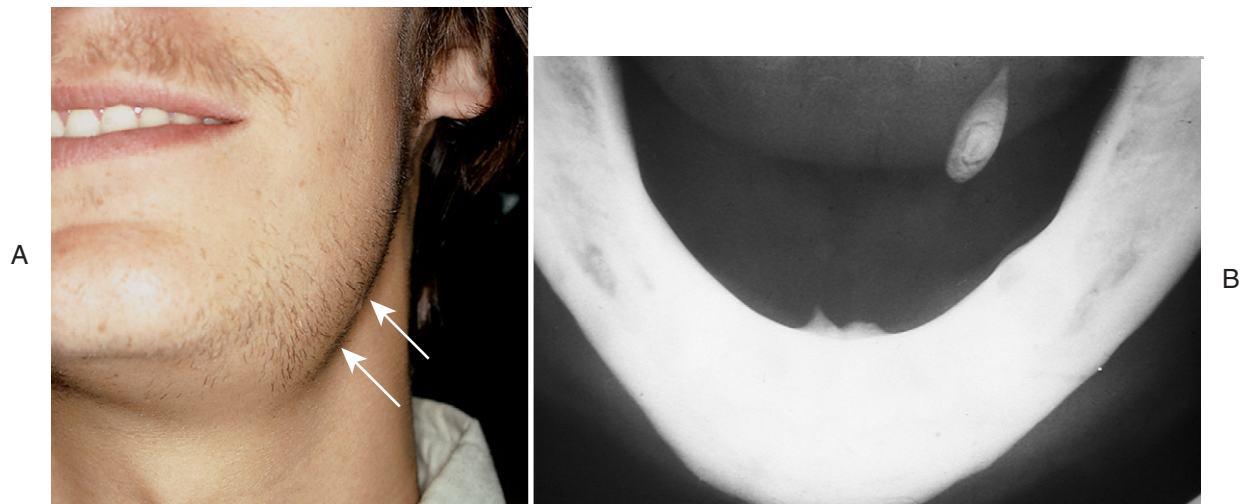


FIGURE 10-11

Submandibular sialolithiasis. **A**, Swelling below the mandible (*arrows*), indicative of mucous retention and sialadenitis of the submandibular gland. **B**, Occlusal radiograph disclosing an oval stone in Warthin duct.

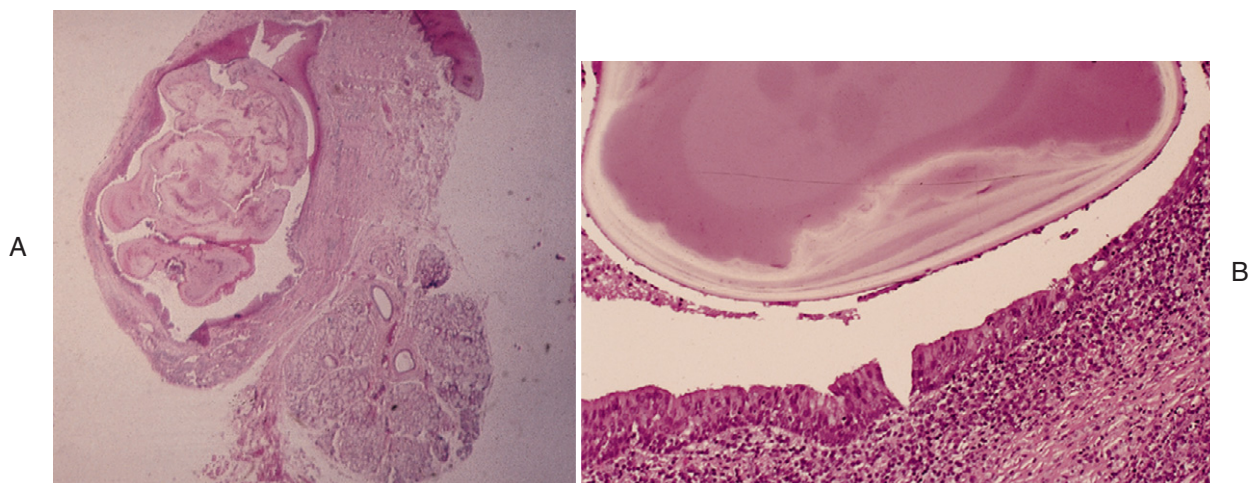


FIGURE 10-12

Sialolithiasis. **A**, Low-power photomicrograph of a large sialolith completely blocking a distended excretory duct of a minor salivary gland. **B**, Medium-power photomicrograph of a portion of a sialolith that exhibits lamination. The ductal wall is infiltrated by leukocytes.

show degenerative changes with the dilatation of intralobular ducts. At this stage, lymphocytic and plasmacytic infiltration is spotty and some acinar degeneration may be present within lobules. As more pressure changes evolve, the ductal ectasia becomes more pronounced and acinar atrophy progresses with few secretory units remaining. Instead the lobules become intensely infiltrated with mononuclear cells, and the ducts remain intact yet dilated. Eventually the infiltrate wanes and the lobules become progressively collagenized. Obstructed glands that become complicated by retrograde acute bacterial sialadenitis show tissue infiltration by neutrophils with purulent material in the ductal lumens.

TREATMENT

Many major salivary gland sialoliths can be removed by manual manipulation of the stone through the major duct orifice. When manual maneuvers fail, a surgical cut-down into the main duct is needed. Intraglandular stones, multiple stones within the gland proper, diffuse glandular calcifications, and long-standing obstructions will usually require removal of the stone in addition to sialoadenectomy. Minor salivary gland stones are well localized and are best treated by simple surgical excision of the stone and the surrounding ductal and minor salivary gland lobular tissues. When signs and symptoms of an acute pyogenic infection exist, incision and drainage with antibiotic therapy should precede or accompany sialoadenectomy.

CHRONIC SCLEROSING SIALADENITIS

SIALADENITIS: *An inflammatory response of salivary gland tissue to a wide spectrum of causative factors.*

CHRONIC SCLEROSING SIALADENITIS: *Chronic inflammation of salivary gland tissue resulting in replacement of acini by lymphocytes, plasma cells, and fibrous tissue but sparing much of the ductal architecture.*

An inflammation of either a major or minor salivary gland is termed *sialadenitis*. Most are chronic, result in the formation of a substantial amount of fibrous replacement of parenchyma, and occur as a consequence of mucous extravasation or duct blockage from salivary stones. In addition, direct trauma or compression of the glands, ducts, or both can cause sialadenitis. In addition to injuries, hyperplasias and neoplasms can lead to a secondary glandular inflammation. Regardless of the source or cause, when degeneration with fibrous replacement and chronic inflammation occurs, the process is referred to as *chronic sclerosing sialadenitis*.

CLINICAL FEATURES

Chronic sclerosing sialadenitis is most often the consequence of direct compression or ductal obstruction. The clinical features of obstructive salivary disease that are reactive to sialoliths and mucous extravasation have been discussed. The obstructed major salivary gland becomes enlarged because of the accumulation of secretions within the duct system and later as a consequence of inflammatory cell infiltration (Figure 10-13). The enlarged gland is generally firm yet freely movable. The firmness may increase with time as fibrotic replacement of acini increasingly occurs. In the minor salivary glands, various surface epithelial proliferations such as papilloma or squamous cell carcinoma and submucosal fibrous enlargements such as fibrous hyperplasia may obstruct the minor duct lumen or compress the extralobular ducts that exit from the gland proper. The flanges of dental prostheses, if overextended, can compress minor salivary glands in the vestibule, resulting in a sialadenitis. In addition, salivary gland neoplasms can compress adjacent normal glands, resulting in obstruction. As a consequence, minor gland chronic sclerosing sialadenitis will evolve, although it may not be clinically obvious.

One of the major causes of sialadenitis is radiation therapy used to treat head and neck cancer. The radiation ports often include the major salivary glands within the treatment field, particularly when the cancer



FIGURE 10-13

Sialadenitis. Sialogram shows an enlarged submandibular gland with prominent ductal ectasia.

is located in the oral cavity or oropharynx. Destruction of acini occurs early in the course of radiotherapy. When dose levels reach 50 centigray, most secretory function will be lost. In these early phases, acinar cell destruction begins and is accompanied by an increase in serum amylase. After a full course of radiation, exposed glands ultimately lose much of their acini and become fibrosed. This usually results in a permanent loss of secretory activity (xerostomia) and leads to cervical caries, oral mucositis, and candidiasis.

HISTOPATHOLOGY

The microscopic changes that are typically found in the affected glands of patients with sialolithiasis are also present in chronic sclerosing sialadenitis caused by other factors (see Figure 10-2). The acinar units degenerate as mononuclear leukocytes, chiefly plasma cells and lymphocytes, infiltrate the lobules. In radiation sialadenitis the earliest changes include loss of secretory granules and cloudy swelling with edema of the acinar cells; neutrophilic infiltration, soon followed by mononuclear infiltration, also takes place. With time all acini are lost and the gland is no longer functional. The ductal elements remain intact, showing ectasia and sialodochitis, whereas the parenchyma becomes progressively fibrotic. These glands, particularly the major salivary glands, may then be subject to retrograde bacterial acute sialadenitis.

TREATMENT

The primary cause of the sialadenitis must be identified before treatment can be initiated. Sources of irritation and obstruction must be removed. If it is ascertained that a major salivary gland is no longer functional, it can be surmised that parenchymal destruction is complete and the gland is fibrosed. Because these glands are prone to acute infections within the persistent duct tree, sialoadenectomy will be necessary.

Complete loss of salivary function as a result of the chronic sclerosing sialadenitis that occurs after radiation therapy has many attending complications. The chief dental complication of xerostomia is root caries. Daily fluoride gels should be prescribed, and meticulous oral hygiene must be instilled. Saliva substitutes offer some benefit for the dryness; if some degree of salivation persists, electrostimulatory devices may increase salivary flow. Pilocarpine may also stimulate salivary flow when not all acinar units are destroyed.

NECROTIZING SIALOMETAPLASIA

NECROTIZING SIALOMETAPLASIA: A spontaneous condition of unknown cause, usually of the palate, in which a large area of surface epithelium, underlying connective tissue, and associated minor salivary glands become necrotic while ducts undergo squamous metaplasia.

Necrosis as the result of obstructive disease of the salivary glands generally occurs slowly. In necrotizing sialometaplasia, acute necrosis of entire lobules of minor salivary tissue occurs in a short period. It is believed that this process is due to infarction. Although the cause of infarction is unknown and is unrelated to systemic microvascular occlusion or thromboembolic disease, the preservation of cellular outlines, characteristic of the coagulative necrosis seen in infarction, is evident in this disease. Importantly, this benign, spontaneously healing lesion may be mistaken (clinically and microscopically) for a malignant salivary gland neoplasm.

CLINICAL FEATURES

Usually located at the hard and soft palate junction, necrotizing sialometaplasia is characterized by a deep-seated ulceration that generally lacks a raised or rolled border (Figure 10-14). Instead the ulcer is punched out and within its deep crater are gray, granular lobules that represent necrotic minor salivary glands. The ulcer often measures 2 to 3 cm in diameter. Although some patients complain of numbness or burning pain, others are completely asymptomatic. The palate is the most common site of involvement, and in most cases the ulcer evolves spontaneously without antecedent trauma. However, a few reports have mentioned occurrence after a local palatal anesthetic injection. The lesion rarely occurs in other sites but has been reported in the tongue, retromolar pad, nasal cavity, antrum, and major salivary glands. In these non-palatal sites the disease is often traced to a cause such as surgery, trauma, or radiation. Experimental replication of the process in laboratory animals supports the fact that ischemic necrosis accounts for the pathologic features. Ligation of vessels reducing blood supply to the salivary glands recapitulates the same microscopic changes that occur in human tissue.

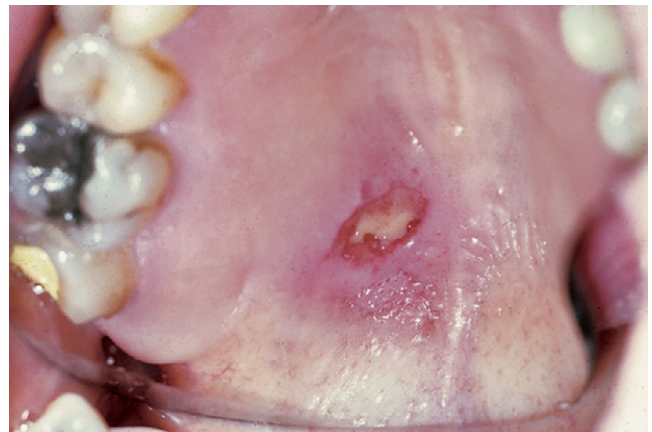
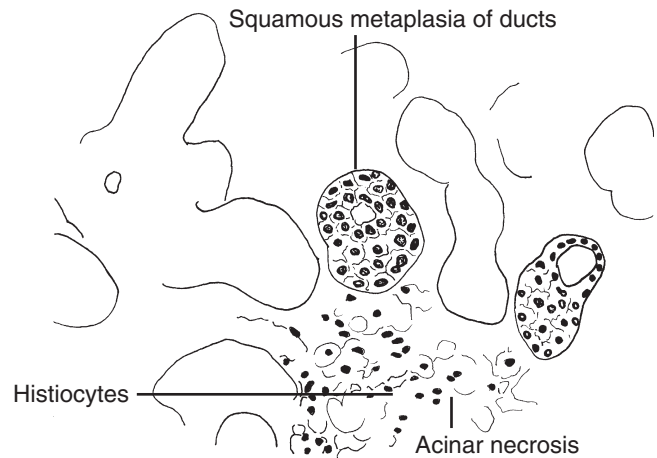
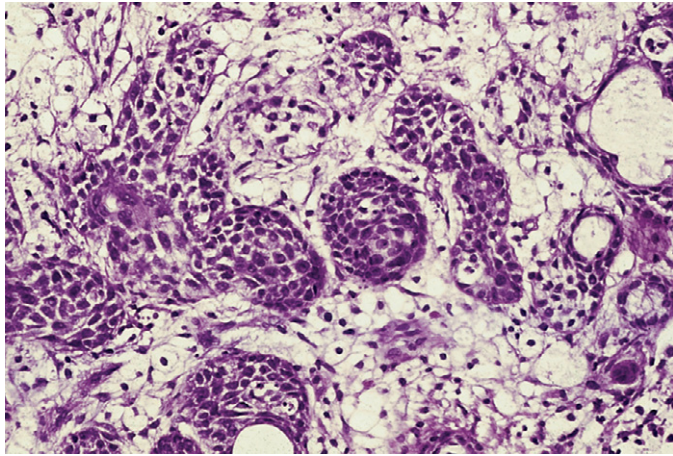


FIGURE 10-14
Necrotizing sialometaplasia. Lesion in typical location appearing as a deep ulcer of the palate.

**FIGURE 10-15**

Necrotizing sialometaplasia. Ductal structures undergo transformation from cuboidal to squamous cells (squamous metaplasia) yielding nodules of epithelium; acini cells undergo necrosis.

Most cases of necrotizing sialometaplasia occur in adults who have a broad age range and a mean age of about 47 years, although women seem to be affected at a somewhat younger age. Males are afflicted slightly more often than females.

HISTOPATHOLOGY

The microscopic features are distinctive and specific. In the palate the surface epithelium is lacking in the zone of ulceration and is replaced by fibrin and granulation tissue. Lobules of minor salivary acini that exhibit features of coagulation necrosis underlie this thin granulation tissue covering. The cytoplasmic borders of the cells of the acinar bulbs are intact. These acinar cells lack nuclei, are distended, and appear pale and basophilic. Entire lobules are similarly affected, with the result that the lobular architecture of the minor salivary glands is still maintained although the cells are nonvital.

Scattered neutrophils and foamy histiocytes are often found in the zones of necrosis where mucin has accumulated or leaked from the necrotic acinar cells. Dispersed around the periphery of the necrotic lobules are ductal elements, many of which show squamous metaplasia (Figure 10-15). These metaplastic foci are typically represented by round or oval epithelial islands composed of benign squamous cells. Lumens are no longer evident in most of these islands. This represents a reactive process akin to pseudoepitheliomatous hyperplasia. Although some of the squamous islands are surrounded by necrotic *ghosts* of acinar elements, others show an enveloping fibrous stroma. The histologic features are similar to those encountered in mucoepidermoid carcinoma. In the latter case the epithelial

component is not oriented into multiple round or oval islands; instead, more diffuse anastomosing sheets of squamous cells are encountered and surround the luminal spaces. Mucous, clear, and intermediate cells are also present. Furthermore, mucoepidermoid carcinoma is not associated with lobular necrosis.

TREATMENT

No treatment is necessary once the diagnosis is microscopically confirmed. The ulcerated area heals slowly, usually within 1 to 3 months.

INFECTIONS

ACUTE PAROTITIS

Acute infections of the salivary glands may be of either viral or bacterial origin. Endemic parotitis or mumps is the most commonly encountered form of infectious sialadenitis. Pyogenic bacterial infections are uncommon and may be seen after major abdominal surgery or in glands that have been obstructed. Chronic infections such as tuberculous sialadenitis and cat-scratch fever are rarely encountered.

VIRAL ENDEMIC PAROTITIS (MUMPS)

Viral or endemic parotitis is an acute sialadenitis caused by an RNA virus of the Paramyxoviridae family, referred to as the *mumps virus*. Other viruses may infect the salivary glands, including the cytomegalovirus (salivary inclusion disease), coxsackieviruses, echovirus, and influenza and parainfluenza virus; however, the mumps virus is the main cause of acute parotitis.

CLINICAL FEATURES

Airborne droplets transmit the mumps virus. It primarily affects the parotid glands but may also infect the submandibular gland. Children between the ages of 5 and 18 are most often infected with this disease, which tends to become epidemic. Once exposed, patients will manifest the disease in 2 to 3 weeks. Onset is characterized by rapid bilateral swelling of the parotid gland with acute pain, particularly during salivation (Figure 10-16). The earlobe is often elevated from the underlying glandular enlargement. A purulent exudate can sometimes be expressed from the main parotid duct orifice but is usually clear and unremarkable. As acini become infected, salivary amylase leaks into the interstitium and is absorbed into the blood stream, thereby raising serum levels of the enzyme. Complement-fixing antibodies to the mumps "S" and "V" antigens can be assayed to confirm the diagnosis. The disease usually persists for 7 to 10 days. Although most cases are uncomplicated, some individuals experience dissemination to the testis or develop encephalitis with attending deafness. Severe forms of mumps orchitis can result in sterility. Because most children in industrialized countries are vaccinated against mumps, the disease is only rarely encountered.

HISTOPATHOLOGY

In mumps the acini develop cloudy swellings and the interstitial connective tissue becomes edematous and infiltrated with plasma cells and lymphocytes. Ductal

ectasia is a feature, and the lumens often contain desquamated cell debris and leukocytes. In acute bacterial sialadenitis, the interstitial regions are infiltrated by neutrophils and the ductal lumina also contain necrotic material and neutrophilic leukocytes. Acinar cell degeneration and necrosis can also be seen.

TREATMENT

No effective antiviral agents exist for the treatment of mumps. Patients are given analgesics and antipyretics to control pain and fever. A liquid diet with vitamin supplementation should be considered in addition to bed rest. Acute bacterial sialadenitis should be managed with antibiotic selection based on sensitivity testing. Under local anesthetic, probing and dilatation of the main duct exiting the gland may facilitate drainage of purulent exudate.

BACTERIAL SIALADENITIS

Bacterial sialadenitis may occur after major surgery (usually abdominal surgery) (Figure 10-17). Although the predisposition is unknown, it may be related to a



FIGURE 10-16
Endemic parotitis (mumps). Child with painful parotid swelling.



FIGURE 10-17
Bacterial parotitis. Infection causing painful parotid enlargement anterior and inferior to earlobe (arrows).

temporary lack of ductal outflow that can develop with the administration of atropine sulfate while delivering general anesthetics, allowing an ascending infection. Similarly, pyogenic bacteria (usually staphylococci and streptococci) can infect obstructed glands. The gland enlarges and is painful on palpation. In classic cases, purulent exudate can be expressed from the duct orifice. This material should be subjected to culture and sensitivity testing so that the appropriate antibiotic can be selected.

IMMUNE-MEDIATED DISEASES

Autoimmune diseases may have multiorgan involvement or affect only a single organ. When an autoimmune disease affects the major salivary glands (autoimmune sialadenitis), it is usually associated with a similar inflammatory reaction in the lacrimal gland. The immunologic process that occurs within the salivary tissue is chronic and progressive, with the eventual destruction of acini by inflammatory cells. The glands become enlarged bilaterally and are functionally deficient, leading to xerostomia. Xerophthalmia also occurs because the lacrimal glands are similarly affected. The histopathologic pattern is one of infiltration with T lymphocytes that mediate the acinar cell destruction and a reactive proliferation of the ductal epithelium. The tissue changes are a classic process in salivary glands and are referred to as *lymphoepithelial sialadenitis* (LES). It is the hallmark of the multisystem disease referred to as *Sjögren syndrome* (SS).

LYMPHOEPITHELIAL SIALADENITIS

LYMPHOEPITHELIAL SIALADENITIS: *A progressive autoimmune chronic inflammatory process, primarily of the parotid glands, in which dense infiltrates of T lymphocytes replace the acini and the residual ductal elements are stimulated to undergo hyperplasia, forming irregularly shaped islands of squamous epithelium (epimyoepithelial islands).*

Whether gland enlargement is present or not, the tissue changes of LES are usually indicative of eventual development of SS. Lymphoid infiltration has also been associated with multiple salivary cysts in patients with human immunodeficiency virus (HIV) infection. In addition, lymphocytic infiltration of the salivary glands with clinical evidence of parotid gland enlargement may occur in mucosa-associated lymphoid tissue lymphoma (MALToma).

When sarcoidosis involves the parotid glands (Heerfordt syndrome), a painless bilateral enlargement also occurs, mimicking SS clinically. Histologically, sarcoidosis differs greatly from LES in that the salivary parenchyma is replaced by noncaseating granuloma-

tous inflammation consisting of macrophages and multinucleated giant cells.

SJÖGREN SYNDROME

SJÖGREN SYNDROME: *A group of autoimmune conditions with a marked predilection for women; it has an intense T lymphocyte-mediated autoimmune process in the salivary and lacrimal glands as one of its most prominent components.*

SS exhibits progressive T lymphocyte infiltration and replacement of the glandular parenchyma that leads to xerostomia and xerophthalmia. The characteristic histologic appearance is that of LES. The hypersensitivity reaction in the parotid and lacrimal parenchyma is considered to be a cell-mediated immunologic reaction to native antigens on specific glandular epithelial cells. This reaction accounts for the dryness that eventually develops in the eyes and oral cavity, the so-called *sicca* (dry) complex. Other autoimmune diseases such as rheumatoid arthritis, scleroderma, lupus erythematosus, and mixed collagen disease may be an accompaniment.

CLINICAL FEATURES

SS occurs in 0.5% to 1.0% of the population; although the disease is not hereditary, associations with certain HLA genotypes have been noted (HLA-B8 and HLA-DR3). More than 80% of patients with SS are women. If the disease affects only salivary and lacrimal glands without other coexisting systemic autoimmune diseases, it is termed *primary* SS. Patients will show keratoconjunctivitis sicca, characterized by corneal keratotic lesions that stain pink when rose bengal dye is used. Tear meniscus and breakup time are reduced. The Schirmer test is used to assess lacrimal flow and is positive when the flow is reduced to less than 5 mm during a 5-minute sample period. This test uses a strip of filter paper that is placed between the eye and the eyelid to determine the degree of tearing, which is measured in millimeters.

Secondary SS occurs when other signs or symptoms of autoimmune disease are present, the most common being rheumatoid arthritis. Other collagen-vascular diseases may occur in secondary SS, including lupus erythematosus, systemic sclerosis, dermatomyositis, and mixed connective tissue disease. Other extrasalivary and lacrimal diseases that have been identified in both primary and secondary forms of SS include Raynaud disease, interstitial nephritis, interstitial pneumonitis, purpura, and polymyopathy. The risk for the development of extrasalivary malignant lymphoma is increased. Specific laboratory findings are most often encountered in secondary SS and include an elevated

erythrocyte sedimentation rate, hypergammaglobulinemia, and positive serologic tests for rheumatoid factors, antinuclear antibodies (ANAs), and anti-Ro (anti-SS-A) and anti-La (anti-SS-B).

The basic cause of SS is unknown. The signs and symptoms of dryness and swelling are the result of the immunologic reaction that occurs in the parenchymal tissue with consequential acinar loss and lymphocytic infiltration. The antigens that stimulate this immune mechanism are not well defined. A viral origin has been suggested whereby immunologic responses to viral proteins cross-react with host cell proteins in salivary epithelia (molecular mimicry). Some evidence suggests that a retrovirus may be involved.

Parotid gland enlargement is observed in approximately 45% of SS patients, and the glands feel firm yet doughy (Figure 10-18). When enlargement is seen, it is usually bilateral. The parotids are the primary major salivary glands to be involved; some patients also have submandibular gland involvement. Imaging with contrast sialography, pertechnetate scintigraphy, computed tomography (CT), or magnetic resonance imaging (MRI) will often assist with the diagnosis, because these techniques will usually demonstrate inflammatory rather than neoplastic imaging features. However, none of these imaging techniques are specifically diagnostic for SS, because any sialadenitis may reveal the same features. Despite the progressive loss of acini and secretory activity, it is rare for the salivary glands of SS patients to develop an acute bacterial sialadenitis. A sialogram reveals a characteristic appearance of pooling of the

opaque dye that resembles shotgun pellets throughout the gland (Figure 10-19).

The manifestations of SS that are of most significance to the patient are dry mouth (xerostomia) and dry eyes (xerophthalmia). The dry sensation is very annoying, because the mucosa in both the mouth and the eyes become thinned, inflamed, and painful with a burning sensation. The dry mucosa is also very susceptible to candidiasis. One of the major consequences of xerostomia is the predilection for root caries, usually at the cemento-enamel junction (CEJ) on the facial aspects of the teeth.

Biopsy of the labial mucosa minor salivary glands has proven to be a reliable adjunct in the diagnosis of SS. This simple procedure requires a sample of six to eight minor salivary gland lobules harvested from the lower lip. Lymphocyte aggregates within the minor glands are enumerated to generate a focus score. The diagnosis of SS is supported when the focus score exceeds that of normal glandular tissue.

HISTOPATHOLOGY

The microscopic features of SS are those of LES, the pathologic hallmark of SS in the parotid gland. Although immunomarker studies have identified the presence of both B and T lymphocytes, the latter are the most abundant. With increasing numbers of infiltrating lymphocytes, progressive destruction and loss of acinar units takes place. Once entire lobules have been infiltrated, it is not uncommon for germinal centers to form with a surrounding mantle of small lymphocytes resembling



FIGURE 10-18
Sjögren syndrome. Patient exhibits bilateral parotid enlargements.

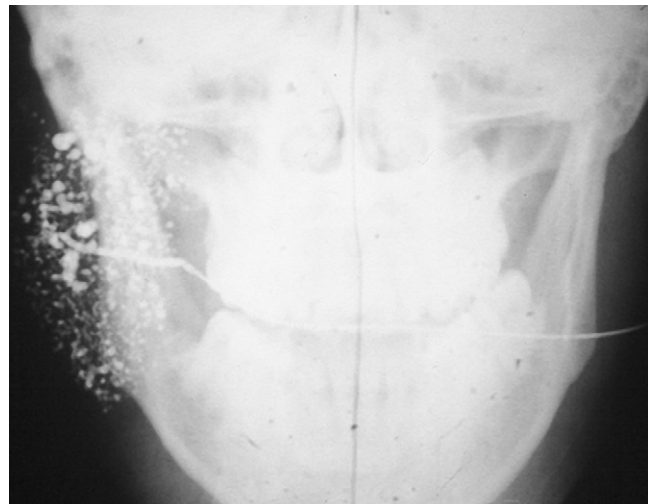


FIGURE 10-19
Sjögren syndrome. Sialogram of parotid enlargement of patient exhibiting characteristic pattern of pooling of dye in areas of damage to the ductal architecture.

lymphoid hyperplasia in a node. These infiltrating cells do not cause lysis of the ductal elements; indeed, the ductal and periductal myoepithelial cells undergo hyperplasia, resulting in islands of epithelial cells that no longer contain well-defined ductal lumens. These epithelial foci are termed *epimyoeplithelial islands* (Figure 10-20, A). The combination of acinar loss, lymphocytic infiltration, and epimyoeplithelial islands constitute LES. MALToma, a specific form of malignant lymphoma of mucosa-associated lymphoid tissue (MALT), may show similar features; the infiltrating lymphocytes are histiocytoid or plasmacytoid and immunohistochemical markers are positive for B lymphocytes (see Chapter 12).

The histopathologic changes seen in the minor salivary glands in SS consist of aggregates of lymphocytes oriented around intralobular ducts (Figure 10-20, B). Normal salivary glands show very few lymphoid foci, and those that are present are composed of only a few cells. Foci with more than 50 lymphocytes are significant; when one or more of these aggregates is identified in a 4 mm² area of glandular parenchyma, a diagnosis

of SS is supported. These lymphoid foci are primarily composed of T lymphocytes.

TREATMENT

No effective therapy exists for SS. Unfortunately the dryness becomes progressively worse, although some patients retain some degree of secretory function. The complications of xerostomia are difficult to treat satisfactorily, but the patient can be helped to cope with the discomfort. The development and progression of root caries can be minimized by daily application of topical fluoride gels and meticulous dental hygiene.

Candidiasis can be managed with the use of antifungal medications. Salivary substitutes or lemon-flavored glycerin and water can be carried and constantly sipped to offer some relief for the sensation of dryness. Pilocarpine and transcutaneous neurostimulatory devices may stimulate secretions in those patients who retain some degree of secretory function. Secondary SS with accompanying collagen diseases will often require additional forms of therapy, including immunosuppressive agents.

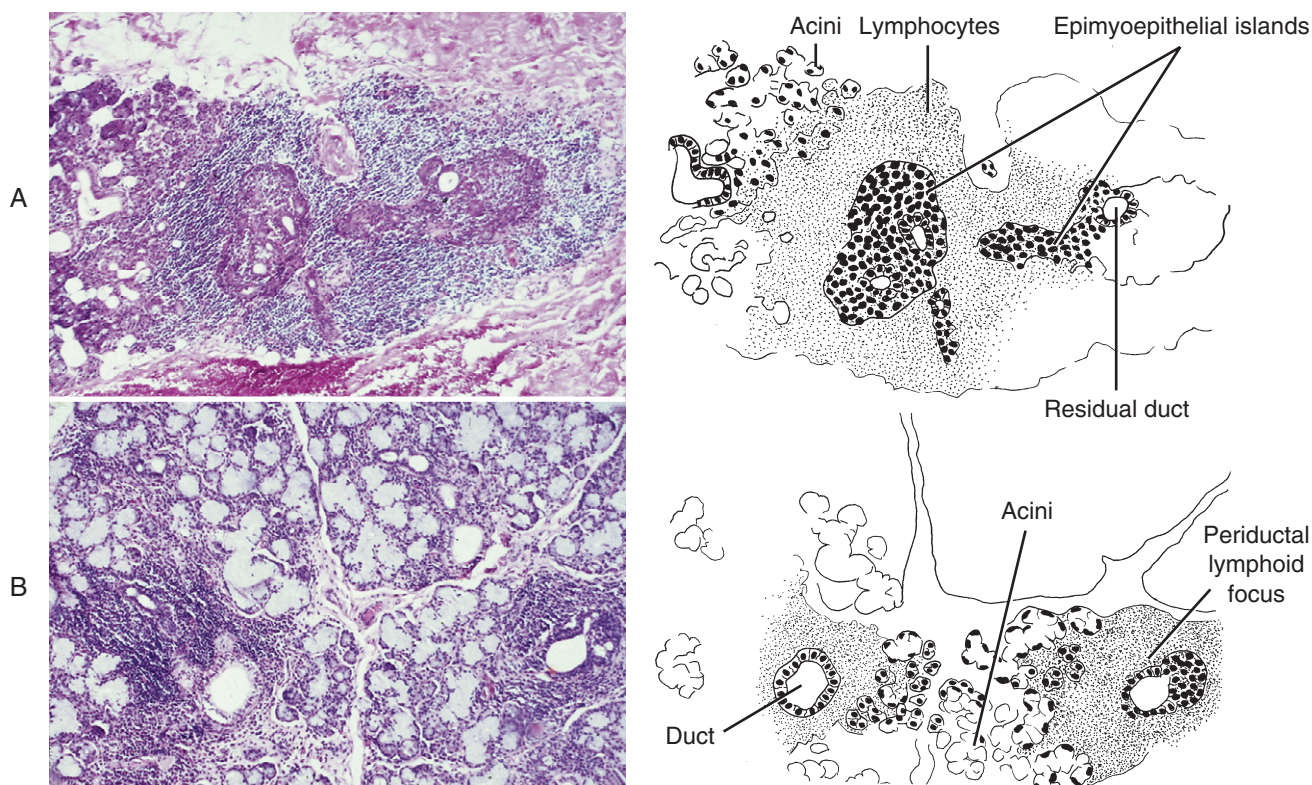


FIGURE 10-20

Benign lymphoepithelial lesion in Sjögren syndrome. **A**, Lymphocyte replacement of acini with formation of epimyoeplithelial islands. **B**, Periductal lymphoid aggregates in a lower lip minor gland.

SALIVARY GLAND TUMORS

The tumors that arise from salivary glands may be derived from salivary epithelium (parenchymal) or the supportive stroma (mesenchymal). The stromal, or mesenchymal, tumors are generally seen in children; most are benign neoplasms of vascular or fibrohistiocytic origin. The parenchymal tumors may occasionally be encountered among children but more often arise during adulthood. Salivary gland tumors affect one to three individuals per 100,000 population, except for northern native peoples, who experience a fivefold to tenfold increase in risk. The major glands account for over 70% of all salivary gland tumors; less than 30% arise in the minor glands (Table 10-2).

As a group the benign parenchymal tumors are **adenomas**, whereas malignant salivary gland tumors are classified as **adenocarcinomas**. These tumors may arise

in patients at any age; the majority is encountered in the fifth to seventh decades. Females are afflicted more often than males. In the parotid gland almost 70% of salivary parenchymal tumors are benign adenomas, whereas tumors arising in the submandibular gland and minor glands of the oral, nasal, and paranasal sinus cavities show an equal predilection for benign and malignant tumors. Intraoral minor salivary tumors are most often encountered in the palate, followed by the upper lip and buccal mucosa. Although palatal and buccal mucosa glands harbor as many malignant as benign tumors, the lip neoplasms are more often benign adenomas. Salivary tumors arising from glands located in the tongue, lower lip, and retromolar areas are more often adenocarcinomas.

Salivary tumors may arise from any of the cellular components of the glandular tree, including basal or reserve ductal cells, striated ducts, intercalated ducts, acini, and myoepithelial cells. The various neoplasms are named according to the differentiation of the tumor cells. Some tumors elaborate a wide variety of secretory, ductal, and myoepithelial cells; others are more monomorphic and composed of ductal or acinar cells only. The histopathologic patterns assumed by these salivary tumors are a reflection of their route of differentiation and should not be misconstrued as being indicative of the cells of origin. All salivary tumors arise from salivary epithelia, yet they differ according to the line of differentiation that the cell population follows.

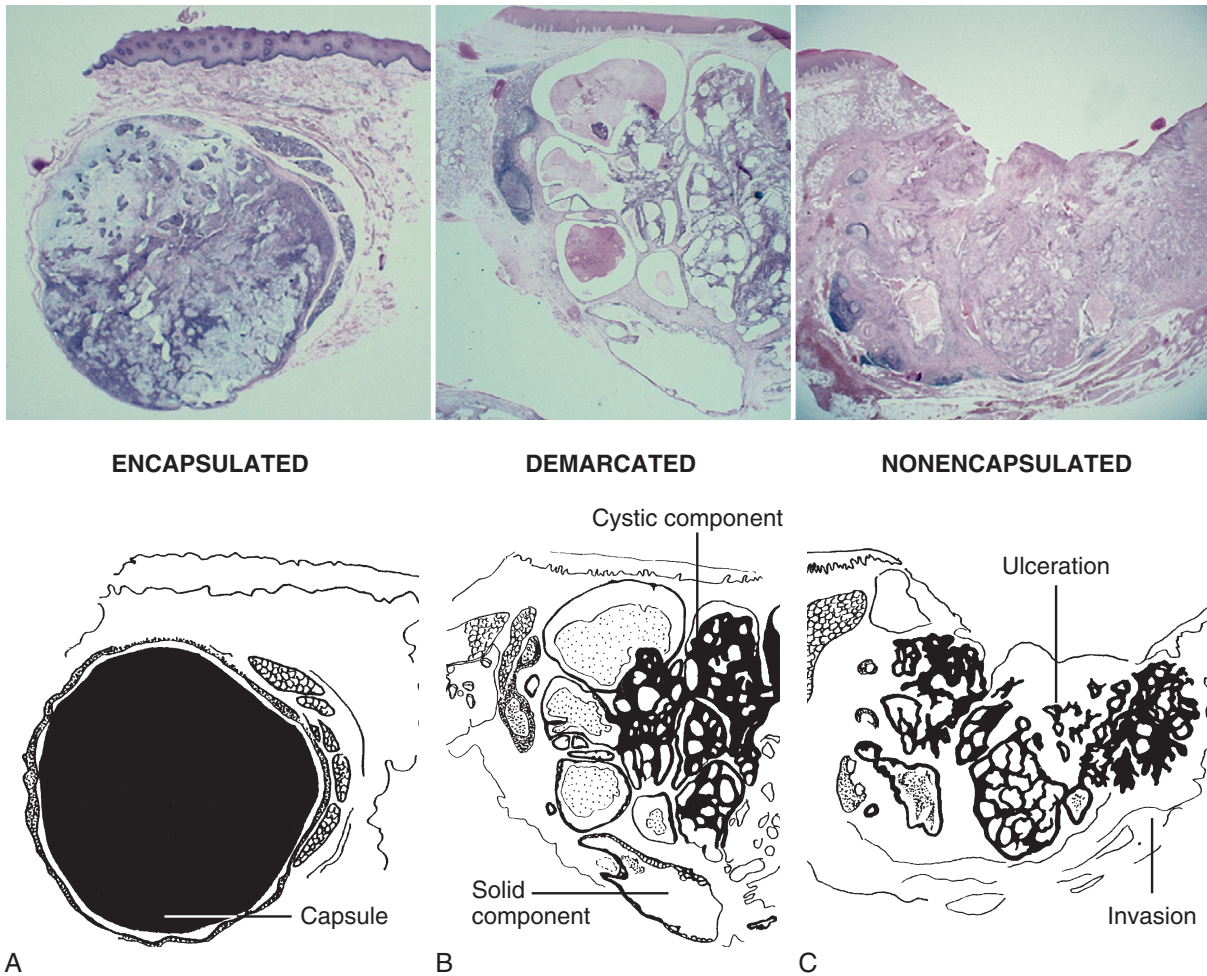
Unlike carcinomas in other locations, such as squamous cell carcinoma, salivary adenocarcinomas usually fail to exhibit significant cytologic anaplasia or atypism. Importantly, most benign adenomas are well demarcated, encapsulated, and not infiltrative. Adenocarcinomas are nonencapsulated and collectively show evidence of invasion into adjacent connective tissue (Figure 10-21). The diagnosis is made based on growth pattern characteristics and differentiation features. As a group, salivary adenocarcinomas are capable of locally aggressive behavior with a tendency for recurrence after treatment; they may metastasize via lymphatic routes, hematogenous routes, or both (Table 10-3).

Table 10-2 Anatomic Distribution of Benign and Malignant Salivary Gland Tumors

	Benign	Malignant
MAJOR GLANDS		
Parotid	70%	30%
Submandibular	60%	40%
Sublingual	30%	70%
MINOR GLANDS		
Palate	50%	50%
Buccal mucosa	50%	50%
Upper lip	75%	25%
Oropharynx	60%	40%
Lower lip	40%	60%
Tongue	15%	85%
Retromolar	10%	90%
Floor of the mouth	10%	90%

Table 10-3: Distinguishing Features of Benign and Malignant Salivary Gland Tumors

	Benign	Malignant
CLINICAL FEATURES	Smooth, uniform surface; normal surface coloration; round, dome shaped; intact overlying mucosa/skin; movable; asymptomatic	Nodular surface; surface telangiectasia; irregularly shaped; ulcerated; fixed and indurated; occasional nerve deficits
MICROSCOPIC FEATURES	Distinct and intact capsule; uniformity of cells; tissue structures resemble normal; neoplastic cells displace nerves; normal stroma; no necrotic areas	Lacks encapsulation; cells irregular in size and shape; altered tissue patterns; neoplastic cells invade nerves; lacks sufficient stroma; occasional areas of necrosis

**FIGURE 10-21**

Growth patterns of salivary tumors. **A**, Adenoma (well-demarcated, encapsulated submucosal tumor). **B**, Low-grade adenocarcinoma (multicystic and well demarcated without encapsulation). **C**, Adenocarcinoma showing ulceration and lack of encapsulation and focal invasion.

BENIGN SALIVARY GLAND TUMORS

Among benign tumors, pleomorphic adenoma (PA) is the most common. Monomorphic adenoma, oncocytoma, and papillary cystadenoma lymphomatosum are also relatively common. Rare types of adenomas include sebaceous adenoma, intraductal papilloma, sialadenoma papilliferum, and cystadenoma.

PLEOMORPHIC ADENOMA

PLEOMORPHIC ADENOMA: *The most common of the benign salivary gland tumors, composed basically of a proliferation of myoepithelial cells and a wide spectrum of epithelial and mesenchymal tissue components and surrounded by a distinctive fibrous capsule.*

The most common benign salivary gland tumor is the PA, or mixed tumor. The term *pleomorphic* refers to the wide variation in parenchymal and stromal differentiation shown by the tumor cells and should not be confused with the nuclear pleomorphism exhibited by many malignant neoplasms. On the contrary, the individual cells of PA show bland, normal, and uniform nuclei regardless of their degree of differentiation.

The often-used term, *mixed tumor*, implies that a wide mixture of different tissue types are observed within individual tumors. The term was originally applied because it was thought that the neoplastic growth arose from multiple germ layers that gave rise to the epithelial and mesenchymal components of salivary tissue. It is now documented that this is not the case, because the origin of the varied cellular elements is from the epithelial cell, myoepithelial cell, or both. The myoepithelial cell is present

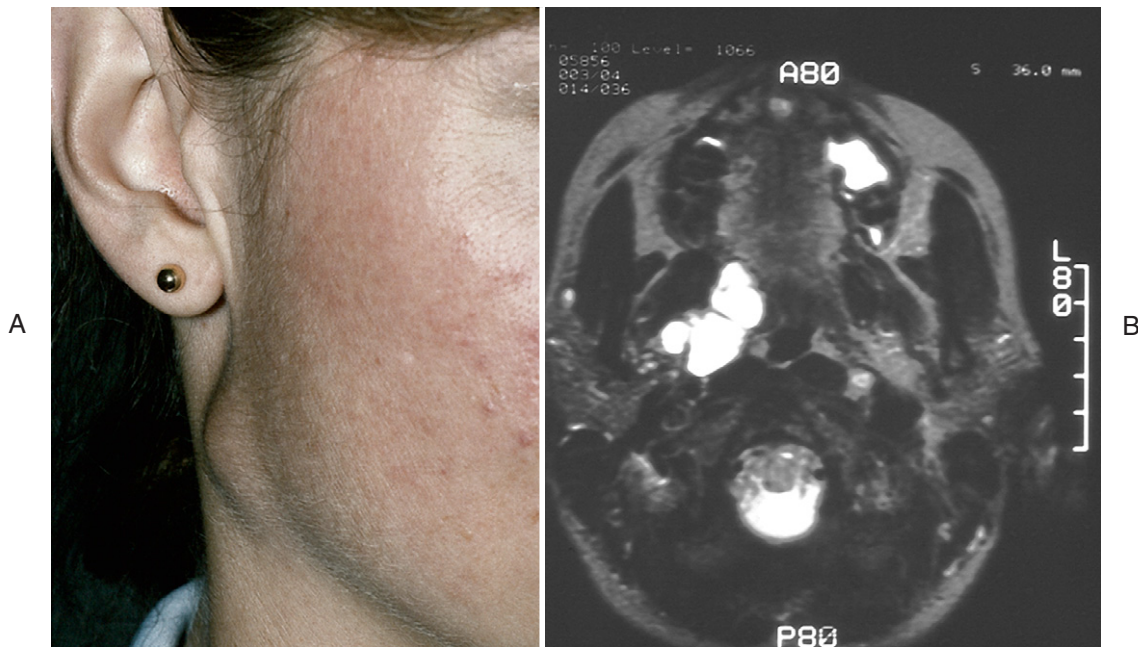


FIGURE 10-22
Pleomorphic adenoma (PA) of the parotid gland. **A**, Clinical appearance. **B**, Magnetic resonance imaging shows a nodular mass of a recurrent PA in the deep lobe of the left parotid gland (*right side of image*).

in periductal locations and has a potential to differentiate into epithelial or connective tissue cell types.

PA accounts for 60% of all parotid gland tumors, 50% of submandibular gland tumors, and only 25% of sublingual gland neoplasms. Fifty percent of all oral minor gland tumors are mixed tumors of which 55% arise in the palate, 25% in the lip (mostly upper lip), 10% in the buccal mucosa, and 10% from all other oral and oropharyngeal sites.

CLINICAL FEATURES

Like other benign tumors, the PA has a slow growth rate and is well delineated. It is soft or only slightly firm on palpation and, in the larger major salivary glands, is freely movable. In the parotid gland the tumor is generally spherical and more often arises in the superficial lobe as an obvious mass anterior to the ear or overlying the angle of the mandible (Figure 10-22). Deep lobe tumors are not always detected as a facial mass, because they may protrude into the lateral wall of the oropharynx.

Occasionally, tumors that have been present for many years will become lobulated or multinodular, a feature shared with tumors that recur after incomplete surgical excision. In the oral minor glands the most common presentation is a soft to slightly firm swelling of the hard or soft palate without ulceration or telangiectasia of the overlying mucosa (Figure 10-23). Al-



FIGURE 10-23
 Pleomorphic adenoma of the palate.

though rare, some palatal PAs will become ulcerated. In the buccal mucosa and lip, PAs are encapsulated, well defined, and movable on palpation. The overlying mucosa is usually intact.

PA is encountered in patients of all ages; however, 60% of the cases occur in the third to fifth decades

(mean age: 40 years). Less than 10% occur in children. The female-to-male ratio exceeds 2:1.

MRI is a reliable diagnostic approach to determining the extent of the disease, particularly in the major salivary glands. The signal is intense, probably owing to the amount of myxoid stroma in these tumors. The images of mixed tumors appear as well-defined spherical or multinodular masses (see Figure 10-22, B).

HISTOPATHOLOGY

The histologic variations, both within an individual lesion and between different PAs, can be extensive. The most constant finding in PA is the presence of a pronounced fibrous capsule (see Figure 10-21, A). This is an extremely important histologic feature when distinguishing benign from malignant salivary tumors. Some lesions of long duration may be multinodular or multifocal; however, a distinct fibrous capsule envelops each nodule or foci. Although the tumor cells may show a wide variation, usually two dominant patterns of differentiation exist: ductal and myoepithelial (Figure 10-24). Many PAs will contain diffuse sheets (medullary pattern) of monomorphic epithelial cells; others appear as interlacing cords (trabecular pattern). Almost all have ductal and tubular elements composed of cuboidal cells oriented around a lumen and associated spindle-shaped myoepi-

thelial cells that appear to spin off the ductal elements. In some tumors the myoepithelial spindle cells are included in a stromal myxomatous pattern, which may constitute its major component. Rarely, squamous differentiation with keratin production and mucus-secreting cells may be seen; these cell types are never predominant.

Sheets of myoepithelial cells in many tumors lose their typical spindle-shaped appearance, becoming polygonal. The polygonal myoepithelial cells often show eccentric nuclei with hyalinized cytoplasm and are referred to as *plasmacytoid myoepithelial cells*. The fibrous stroma usually blends with the spindle-shaped myoepithelial component. In some tumors the stroma becomes densely hyalinized; in others, chondroid, adipose, and even osseous stromal elements are encountered. The wide variation in the stromal elements is thought to evolve from inductive biochemical signals from the salivary epithelial and myoepithelial tumor cells.

Importantly, although PAs are well encapsulated, it is not uncommon for neoplastic nests of cells to perforate the capsule, creating a new tumor focus. This event leads to the multinodularity sometimes observed in these tumors. If the tumors are simply enucleated, extracapsular foci may be incompletely removed, thereby leading to a recurrence. In less than 1% of cases, malignant transformation occurs in PA, especially those that have undergone

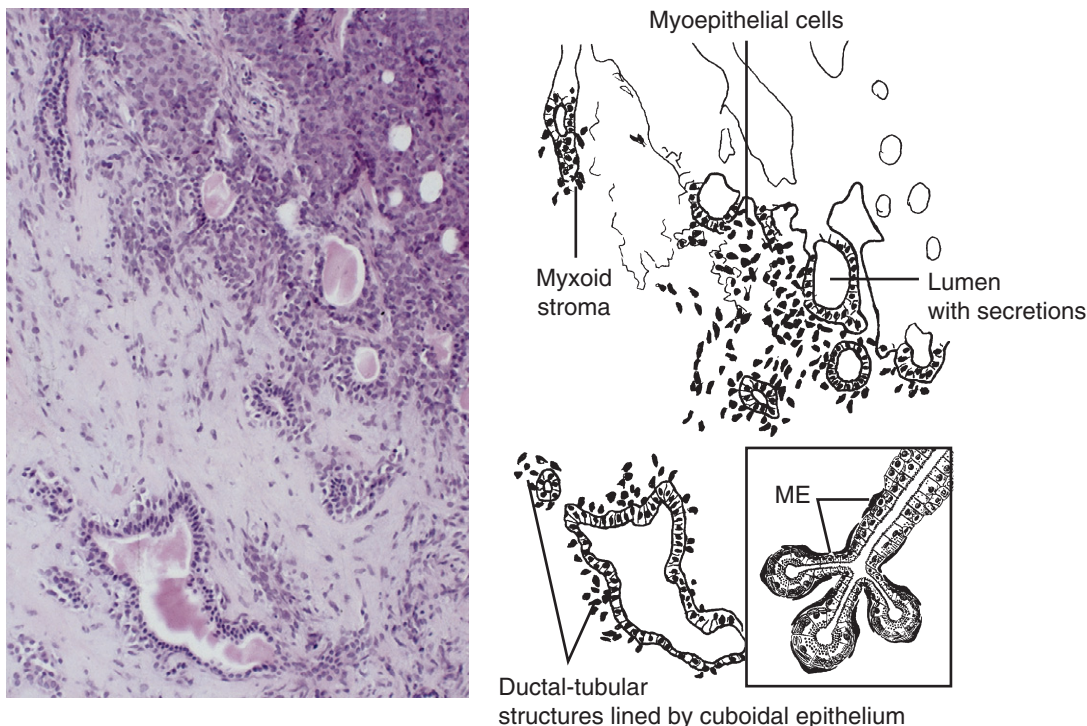


FIGURE 10-24

Pleomorphic adenoma. Cuboidal cells line ductal structures. Myoepithelial cells (ME) are elongated and become loosely dispersed in the connective tissue stroma.

multiple recurrences. These tumors are termed *carcinoma ex pleomorphic adenoma*.

TREATMENT

PAs arising in the major glands are treated by lobectomy or sialoadenectomy. Because recurrences are common as a result of the presence of extracapsular foci of the disease, simple enucleation is contraindicated. For the palatal lesions, overlying mucosa, and underlying periosteum should also be excised. PAs of the lip and buccal mucosa rarely recur after simple enucleation; however, the incidence of recurrence is minimized or eliminated in all locations by excising the tumor with a margin of normal tissue.

MONOMORPHIC ADENOMA

MONOMORPHIC ADENOMA: A group of benign salivary gland tumors composed of a proliferation of a single epithelial cell type that has a distinctive architectural pattern and is surrounded by a well-defined fibrous capsule. The two most common types are basal cell adenoma and canalicular adenoma.

Monomorphic adenomas lack the wide cellular diversity encountered in PAs. They are composed of a single cell type, hence the term *monomorphic adenoma*. Although these salivary gland adenomas are slow growing and encapsulated, similar to PA, they differ by having a lower propensity for recurrence. Two distinct entities in this group can exhibit different clinicopathologic features: (1) **basal cell adenoma**, usually found in the parotid gland, and (2) **canalicular adenoma**, typically located in the submucosa of the upper lip.

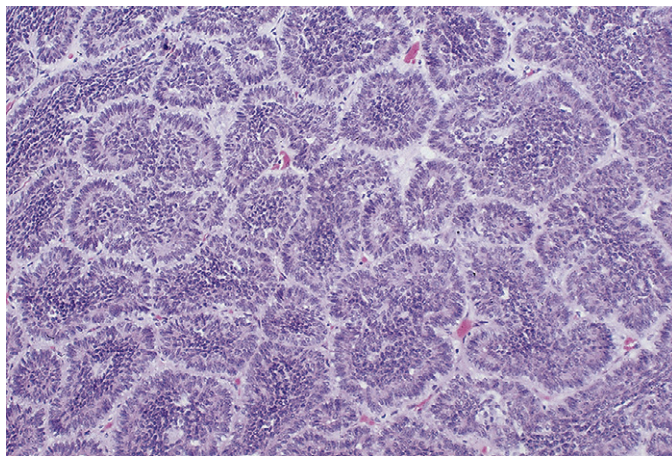
CLINICAL FEATURES

The basal cell adenoma is localized to the parotid gland in 75% of cases. Less than 20% of these tumors are found within the oral cavity; those that arise from intraoral minor glands are usually found within the upper lip and buccal mucosa. The tumor is seen in adults and has a peak predilection for the seventh decade; females are affected more often than males. In the parotid gland these neoplasms are clinically indistinguishable from PAs, because they also tend to arise in the superficial lobe, are well encapsulated, and movable. On palpation basal cell adenomas are firmer than mixed tumors. Most are small tumors less than 3 cm in diameter.

Canalicular adenoma occurs in older patients, commonly in the seventh decade, with females affected more often than males. It rarely occurs in children. Approximately 75% of canalicular adenomas occur in the upper lip. The remaining tumors are found in the buccal mucosa; occurrence in the major glands or other oral minor glands is extremely rare. Most canalicular adenomas are single tumors less than 2 cm in diameter; however, multicentric tumors of the lip salivary glands can occur. They are freely movable and encapsulated. The overlying mucosa is smooth, intact, and usually normal in color but can show a slight bluish tinge.

HISTOPATHOLOGY

A fibrous capsule surrounds the basal cell adenoma. Within the tumor, cells cluster in oval nests that are separated by mature fibrous stroma. The outermost layer of cells that surround each cell nest are usually cuboidal, whereas the more centrally located cells within the cell nests are uniform and resemble basal cells in stratified squamous epithelium (Figure 10-25). In some tumors



Tumor lobules with surrounding basal cells

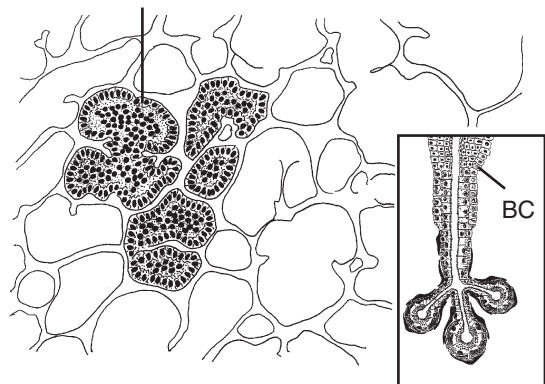


FIGURE 10-25

Basal cell adenoma. This variant of monomorphic adenoma is composed of solid nests of cells rimmed by basal cells (BC).

the individual tumor nests are small and well defined, resembling those seen in basal cell carcinoma of skin. In others, diffuse sheets of basaloid cells may be encountered, with some exhibiting keratin pearl formation. A trabecular pattern may predominate in which elongated anastomosing cords of basal cells are surrounded by mature connective tissue stroma.

Tubular patterns may prevail and are characterized by basaloid nests that surround cuboidal-lined ductal spaces filled with an eosinophilic secretion product. Occasionally, basal cell adenomas show islands of tumor cells that are enveloped by a prominent hyalinized basal lamina, the so-called *membranous* or *dermal analogue adenoma*. This type of adenoma resembles the dermal eccrine cylindroma, hence the term *dermal analogue tumor*. Both salivary and cutaneous tumors may occur together in a given patient.

The canalicular adenoma has a histologic pattern that is usually unique and distinct. It is featured by the presence of a capsule that surrounds the proliferating monomorphic single-layered cuboidal or columnar duc-

tal cells (or both) that are arranged in elongated anastomosing chords (Figure 10-26). The nuclei are oval or elongated and monomorphic. Ductal lumina are often prominent, with the nuclei polarized toward the basement membrane. The stroma is classically myxomatous, composed of an eosinophilic-staining hypocellular mucoid matrix that is traversed by prominently dilated capillaries. The extensive ductal and anastomosing network of cuboidal and columnar cells gives the impression of multiple interconnecting canals, hence the term *canalicular*. Some tumors show cystic areas into which papillary fronds of the canalicular pattern of cells project. Multicentric tumors are occasionally seen; even with single lesions, adjacent salivary lobules may show minute multiple foci of tumor cells surrounded by normal acini.

TREATMENT

Simple excision is the treatment of choice for both basal cell and canalicular types of monomorphic adenoma. It is recommended that the excision include some surrounding normal tissue. Recurrence is uncommon.

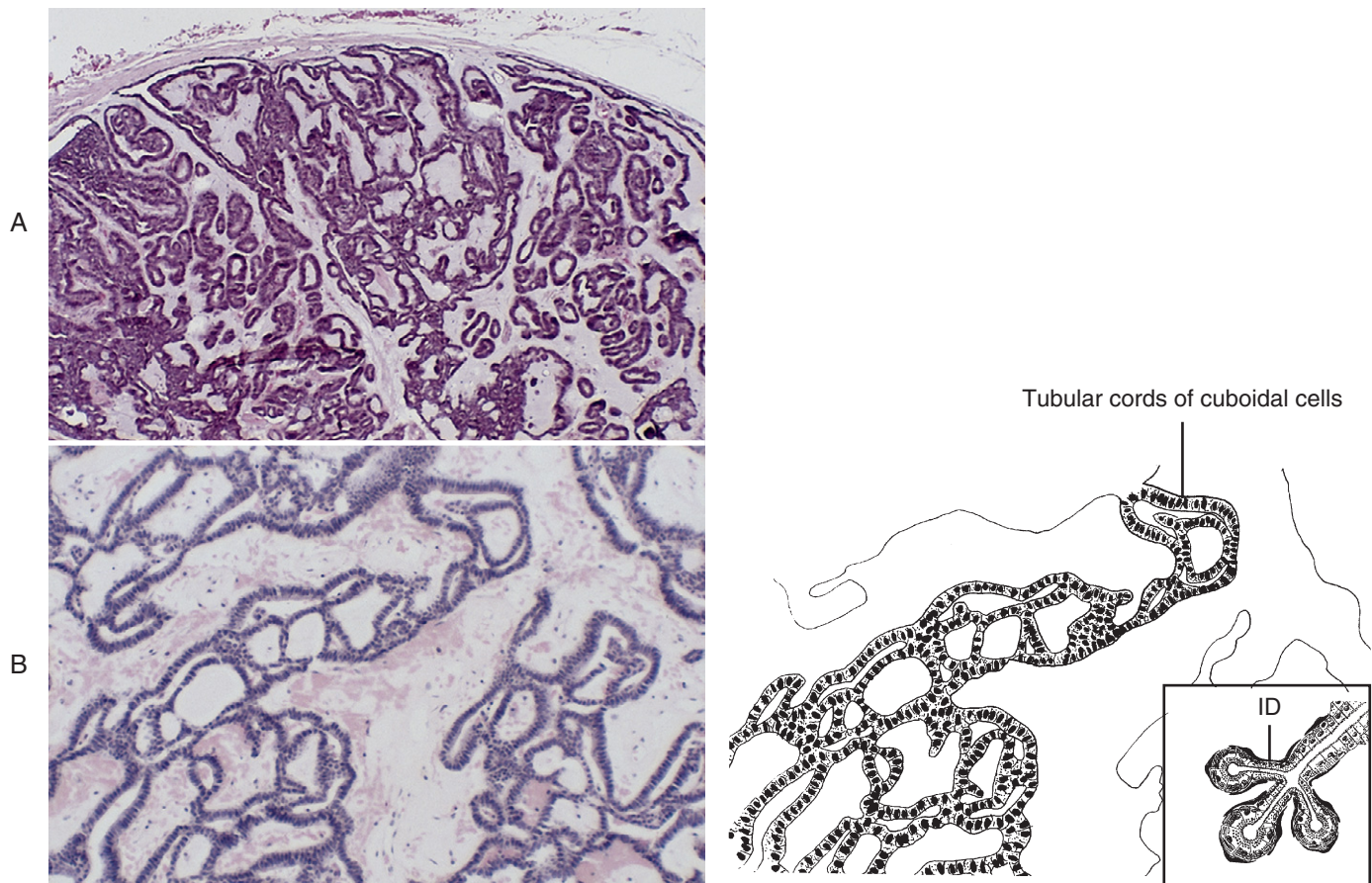


FIGURE 10-26

Canalicular adenoma. **A**, Low-power photomicrograph exhibiting a capsule and cord arrangement of the epithelial component. **B**, High-power photomicrograph reveals the anastomosing cords of cuboidal cells accompanied by a delicate immature stroma typical of this variant. *ID*, Intercalated duct cells.

PAPILLARY CYSTADENOMA LYMPHOMATOSUM

PAPILLARY CYSTADENOMA LYMPHOMATOSUM:

A benign salivary gland lesion with limited growth potential primarily occurring in the tail of the parotid gland; it is composed of cystic spaces with intraluminal projections lined by a double cell layer of eosinophilic columnar cells and contains abundant lymphoid tissue in the underlying connective tissue.

Of all the tumors that occur in the salivary glands, papillary cystadenoma lymphomatosum, also referred to as the *Warthin tumor*, is the most benign with self-limited growth potential. Because of their limited growth, these tumors are considered by most pathologists and clinicians to be hamartomas rather than true neoplasms. The unique aspect of this tumor is the mixture of cystic salivary ductal elements and normal lymphoid tissue. It is proposed by some that the lesion arises from ductal cells that have permeated and proliferated within parotid gland lymph nodes or lymphoid aggregates. Others suggest that the presence of the cystic adenomatous proliferation initiates a secondary lymphoid reactive response in the stroma.

CLINICAL FEATURES

The papillary cystadenoma lymphomatosum primarily occurs in the parotid gland, accounting for about 5% of all parotid salivary tumors. It is extremely rare in other

major or minor glands. Unlike other salivary tumors, it has a slight predilection for males. Most cases are discovered in patients in the sixth and seventh decades of life. Approximately 10% of the cases are bilateral. Multiple lesions within one of the parotid glands are also encountered. The tumor is consistently found overlying the angle of the mandible in the superficial lobe and is well encapsulated and movable. It has a characteristic feel on palpation. When compressed with the fingers, the tumor usually feels doughy. Technetium 99m pertechnetate radioisotope scanning is often helpful, because the tumor readily takes up the isotope and appears as a *hot nodule*.

HISTOPATHOLOGY

Gross examination of a sectioned tumor reveals a characteristic appearance. The tumor has a dense fibrous capsule, with the internal structures exhibiting multiple confluent cystic compartments containing clear, yellow, or brown viscous material. The microscopic appearance demonstrates cystic spaces lined by pseudostratified columnar cells with a very distinct eosinophilic cytoplasm (columnar oncocytes) (Figure 10-27). These cells resemble those normally found in striated ducts of salivary glands and are in a double row, with the nuclei oriented in the basilar area of the bottom row and in the superior aspect of the upper row. These cells cover papillary fronds that extend into the cystic spaces. The papillary fronds are supported by large amounts of lymphoid tissue with widely scattered germinal centers.

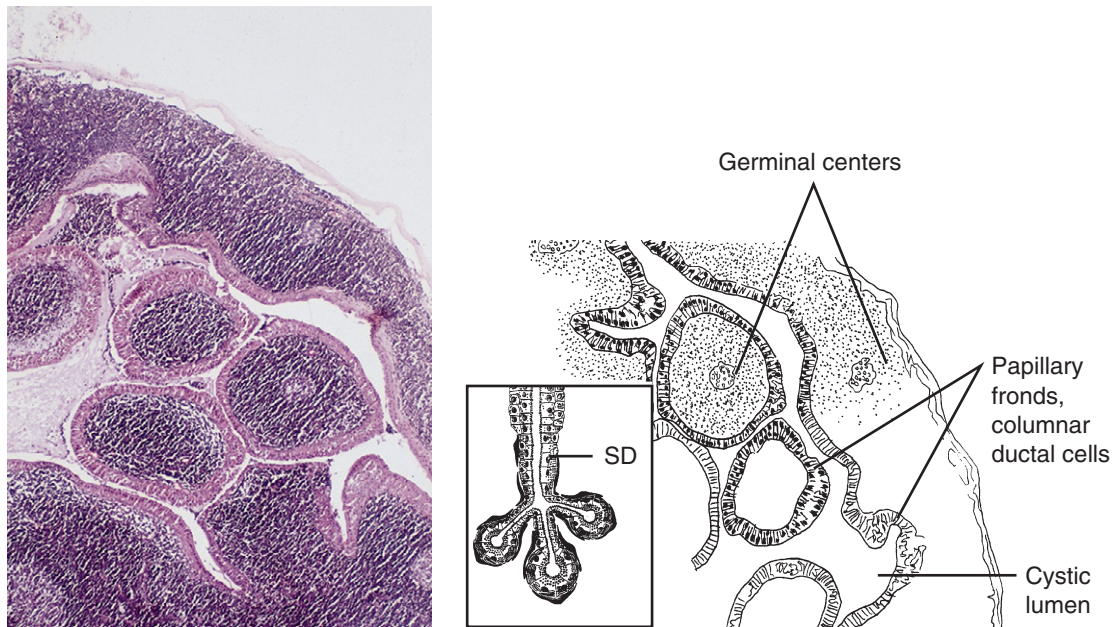


FIGURE 10-27

Papillary cystadenoma lymphomatosum. Present are intraluminal projections (papillary fronds) with an outer two-cell layer covering of eosinophilic ductal cells resembling striated duct cells (SD) and central lymphoid follicles, some with germinal centers.

Rarely, mucous goblet cells are interposed among the oncocytic columnar epithelial cells. Rare cases of malignant transformation into adenocarcinoma have been reported.

TREATMENT

Simple enucleation is probably adequate for most papillary cystadenoma lymphomatosum tumors; however, because of the potential for multicentricity, most surgeons recommend superficial lobectomy to prevent recurrence or emergence of a new tumor at a later time. A true assessment of recurrence rate is difficult to ascertain because a perceived recurrence may simply represent a second new tumor. The rate of recurrence is less than 10%.

ONCOCYTOMA

ONCOCYTOMA: A benign salivary gland tumor occurring primarily in the parotid gland that is composed of clusters of eosinophilic granular cells (oncocytes) containing abundant mitochondria arranged in an organoid pattern and surrounded by an intact fibrous capsule.

An oncocyte is an abnormal cell with a prominent eosinophilic and granular cytoplasm. Occasional oncocytes are found in many other glands; however, when they constitute the primary cell population of a neoplastic process, they are termed *oncocytoma*. The oncocytes are commonly seen in the normal salivary ducts of older patients where they resemble enlarged striated duct cells. The prominent cytoplasmic eosinophilic granules are mitochondria. An oncocyte is essentially an epithelial cell with excessive proliferation of mitochondria. The majority of oncocytomas arise in the parotid gland; only 10% are found in other major salivary glands.

CLINICAL FEATURES

Oncocytoma shows a female predilection and tends to occur in older patients; most tumors arise in the eighth decade. It accounts for only 1% of all salivary gland tumors. The lesion is usually located anterior to the ear or over the mandibular ramus. It may be multinodular but is usually singular. On palpation it appears as a freely movable nodular mass. Occasionally the tumor arises in the deep lobe of the parotid gland, where it may lie adjacent to branches of the

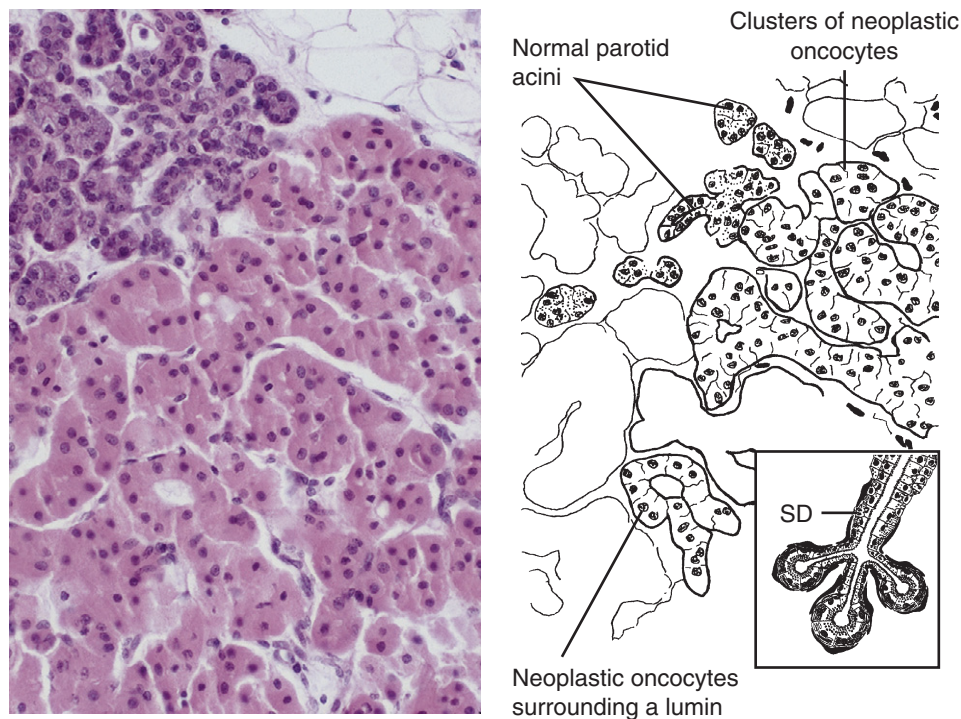


FIGURE 10-28

Oncocytoma. Tumor cells are prominently eosinophilic, granular, and uniform with centrally placed nuclei resembling striated duct cells (SD).

facial nerve. As with papillary cystadenoma lymphomatosum, technetium 99m pertechnetate concentrates in oncocytomas, causing a *hot* appearance during radioisotope scanning.

HISTOPATHOLOGY

Oncocytoma contains a distinct capsule and may have a unilobular or multilobular pattern. The individual cells are polygonal or cuboidal and are usually arranged in an organoid or acinar pattern. Although discrete ductal lumina are not prominent, some oncocytomas have organoid cell clusters that form cords or “doughnut-shaped” circular configurations (Figure 10-28). The cell clusters are characteristic, because they stain intensely eosinophilic. Each cell exhibits a copious amount of granular cytoplasm with centrally placed nuclei (usually small and pyknotic but occasionally vesicular). A characteristic feature is the lack of a fibrous stroma. The tumor cells are clustered, and each cluster is surrounded by fine vascular septae.

A clear cell variant occurs in which the typical granular eosinophilic cytoplasm is not present. The cells in **clear cell oncocytoma** are vacuolated with only wispy remnants of cytosol. The rest of the tumor architecture is identical to the common form of oncocytoma.

TREATMENT

Surgical excision by lobectomy with preservation of the facial nerve is the treatment of choice. Simple enucleation without removal of the entire lobe will result in incomplete removal with recurrence in 10% of the cases.

OTHER ADENOMAS

A variety of less common benign salivary tumors may be encountered in the major and minor salivary glands that have nomenclatures that reflect the type of differentiation exhibited by their microscopic patterns. Three of these are (1) benign papillary growths that arise within the ductal system, (2) salivary adenomas with sebaceous differentiation, and (3) tumors comprised of multiple cystic ductlike spaces (cystadenomas).

CLINICAL FEATURES

In the major salivary glands, the various forms of adenomas tend to be firm, composed of compressible, well-demarcated masses that are movable, because most are encapsulated. In the oral cavity, most adenomas present as submucosal movable nodules. In both major and minor glands, these uncommon forms of adenoma are typically painless. Only the sialadenoma papilliferum appears as an exophytic papillary lesion and closely resembles the common squamous papilloma that arises from the surface stratified squamous epithelium.

HISTOPATHOLOGY

These less common forms of adenoma are classified according to their histologic appearance. The papillary tumors that arise within ductal structures include intraductal papilloma, inverted ductal papilloma, and sialadenoma papilliferum. The intraductal papilloma is a benign proliferation of ductal type columnar cells that line papillary stalks, the core of which is fibrovascular connective tissue. These ductal cells may be oncocytic or exhibit mucous metaplasia; the papillary mass projects into a dilated ductal luminal space. The *inverted ductal papilloma* is so named because of its resemblance to inverted sinonasal papilloma. A flask-shaped invagination of an excretory salivary duct is seen just below the level of the surface epithelium. Inverting papillary acanthotic stratified squamous epithelium shows foci of mucous metaplasia, and the luminally oriented cells may be columnar. In sialadenoma papilliferum, ductal papillary configurations are seen within an excretory duct; as these papillary projections protrude externally, they show keratinocyte differentiation (being stratified squamous).

Sebaceous tumors include the sebaceous adenoma and arise in the major salivary glands (usually the parotid). The tumor cells do not exhibit salivary glandular features but mimic the skin adnexal sebaceous gland epithelium. A variant form resembles papillary cystadenoma lymphomatosum in that the sebaceous acini and ducts that comprise the tumor are found within a lymphoid stroma.

The cystadenomas are characterized by microcystic spaces lined by cuboidal or columnar cells. In some tumors, papillary projections of ductal cells into the lumens of cystic spaces are seen; such tumors are termed *papillary cystadenomas*. These benign salivary tumors may closely resemble sialocysts and reactive changes that accompany ductal obstruction. Benign tumors of salivary stromal connective tissues are rare and tend to occur in children. Common among these tumors are hemangioma and fibroxanthoma.

TREATMENT

All of these various forms of adenomas are slow growing and usually do not recur after excision. Enucleation or simple local excision is the treatments of choice.

MALIGNANT SALIVARY GLAND TUMORS

The most commonly encountered malignant tumors are mucoepidermoid carcinoma, adenoid cystic carcinoma, polymorphous low-grade adenocarcinoma, and acinic cell carcinoma. Rare malignancies arising in salivary glands include clear cell carcinoma, epithelial-myoepithelial carcinoma of intercalated ducts, papillary cystadenocarcinoma, **basal cell adenocarcinoma**,

undifferentiated carcinoma, mucinous carcinoma, malignant **mixed tumor** (PA with cytologic features of malignancy), carcinoma ex mixed tumor (an adenocarcinoma arising from a preexisting benign PA), squamous cell carcinoma of salivary origin, adenosquamous carcinoma, and **salivary duct carcinoma**. Melanoma and lymphoma also occur within the major salivary glands.

All malignant salivary gland tumors are a form of adenocarcinoma. Adenocarcinomas of the salivary glands differ from some of the other groups of adenocarcinomas in the body. Behavioral patterns between each type of adenocarcinoma vary widely; some are almost benign, and others have a very poor prognosis.

MUCOEPIDERMOID CARCINOMA

MUCOEPIDERMOID CARCINOMA: *A malignant salivary gland tumor of varying degrees of aggressiveness, composed of mucus-secreting and stratified squamous (epidermoid) epithelial cells and lacking a capsule.*

Mucoepidermoid carcinoma differs in its general behavior from other adenocarcinomas of salivary gland origin and also by exhibiting distinctive behavioral differences within its own histopathologic spectrum. Consequently, mucoepidermoid carcinoma is subcategorized based on its histopathologic features into *high-grade*, *intermediate-grade*, and *low-grade* varieties; the high-grade type of mucoepidermoid carcinoma is the most aggressively malignant. The neoplastic cells of mucoepidermoid carcinoma differentiate along both mucous cell and squamous cell lines, thereby showing cell types that mimic mucous acinar cells and extralobular ductal cell elements. This malignancy arises in both major and minor salivary glands. On rare occasions it has been found within the mandible where it is thought to arise from odontogenic epithelium.

CLINICAL FEATURES

Mucoepidermoid carcinomas can occur in patients throughout their adult life, with approximately equal numbers occurring from the third to the seventh decades. Although they are occasionally encountered in teenagers, they rarely occur during the first decade of life. A significant female predilection exists, particularly for tumors arising in the tongue and retromolar minor glands. Nearly half of mucoepidermoid carcinomas are found in the parotid gland, and the palate accounts for almost 20%. Of the lesions arising from the minor glands within the oral cavity, almost half of the cases are located in the palate (Figure 10-29). The buccal mucosa, lips, tongue, mandible, and retromolar areas are other favored sites.

In the parotid gland the tumors usually arise in the superficial lobe, where they appear as relatively well-defined focal nodules. They may be movable, which is an

uncommon feature for a malignant lesion. The low-grade lesions are often fluctuant, whereas high-grade tumors are usually indurated and fixed to adjacent tissue. These tumors usually range from 1 to 4 cm in diameter when first diagnosed. Facial nerve involvement, manifested as facial weakness or paralysis, is uncommon but when present is usually a harbinger of a high-grade lesion. Within the oral cavity most low-grade tumors are submucosal masses that have an intact, nonulcerated surface. Low-grade lesions, which are often composed of multiple cystic structures containing mucin, may yield a bluish tinge to the overlying mucosa and are easily mistaken for mucoceles. High-grade intraoral tumors may show surface ulceration. MRI is useful in demonstrating the extent of disease. Low-grade tumors with high mucin content will exhibit a high signal intensity on T2-weighted images.

Central (intraosseous) mucoepidermoid carcinoma of the jaws is most often located in the mandible; however, some maxillary cases have been observed. Approximately 4% of all mucoepidermoid carcinomas arise in the central region in bone. Although some of these tumors are detected because of osseous expansion and clinically evident bony enlargement, others are observed on routine dental radiographs. The central lesions may be unilocular or multilocular radiolucencies, occurring most frequently in the mandibular third molar region. An impacted tooth is often associated with the neoplasm, suggesting a relationship to odontogenic tissue. Unlike other intraosseous jaw malignancies, paresthesia is rarely a complaint.

HISTOPATHOLOGY

Mucoepidermoid carcinomas have three dominant cell types: mucous, epidermoid, and intermediate. These cellular elements are arranged in nests and diffuse



FIGURE 10-29
Mucoepidermoid carcinoma. Lesion of the palate revealing a smooth, nonulcerated appearance similar to a mucocele.

sheets that may surround cystic spaces. A true capsule is generally lacking, although in some regions the leading edge of the tumor is often well demarcated (see Figure 10-21, B). It is common for focal areas to exhibit infiltration into the normal salivary tissue, connective tissue, or muscle. The individual cells show neither significant cytologic features of malignancy nor evidence of increased mitotic activity. Tumors with a preponderance of mucous cells and multiple cystic spaces are classified as *low-grade*; those with more solid islands, fewer mucus-secreting cells, and a high proportion of stratified squamous epithelial (epidermoid) cells are classified as *high-grade* tumors. Intermediate-grade tumors fall between these two extremes.

Low-grade mucoepidermoid carcinoma has limited metastatic potential. Goblet mucus-secreting cells and columnar ductal cells line the multiple cystic spaces (Figure 10-30). Papillary fronds surfaced by both mucous and columnar cells are commonly encountered, with only focal nests of squamous cells that generally lack keratin pearl formation. The tumor islands and cystic structures are separated from one another by a mature fibrous stroma. Commonly the marginal tissue is infiltrated by lymphocytes with occasional germinal center formation. These lymphoid foci seem to be a re-

action to the tumor and should not be confused with metastatic disease to a lymph node.

Intermediate-grade tumors also show cystic spaces; however, they are neither numerous nor large. The so-called *intermediate cells*, which are polygonal but lack true squamous differentiation, are often arranged in diffuse sheets that intervene between the ductal, mucous, and squamous cells.

In high-grade tumors the proliferating squamous cells predominate, few cystic spaces are encountered, and only occasional nests of mucus-secreting cells are noted. The high-grade tumors resemble squamous cell carcinoma to some extent but usually do not show the keratin pearl formation and the severe cytologic atypia of that lesion. Nevertheless, some degree of pleomorphism and hyperchromatism are usually seen in high-grade tumors. A clear cell variant exists and is characterized by sheets of vacuolated cells that fail to stain for mucin. These clear cells merge with the squamous cells. The usual distinguishing features of mucoepidermoid carcinoma are generally found in neighboring fields. The clear cell variant is classified as *intermediate to high grade*.

Central mucoepidermoid carcinoma of the jaws is usually of the low-grade variety. These tumors are believed to arise from odontogenic epithelium, because

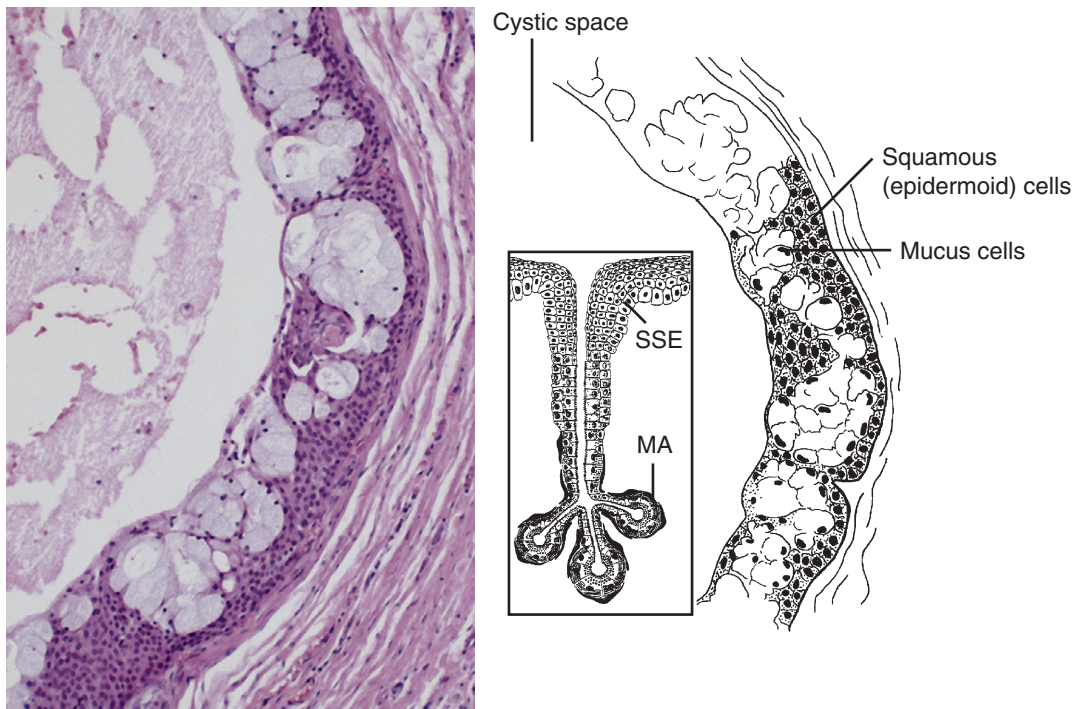


FIGURE 10-30

Low-grade mucoepidermoid carcinoma. A cystic space is lined by squamous (epidermoid) cells and clusters of mucus-secreting cells. SSE, Stratified squamous epithelium of excretory duct; MA, mucus acini.

dentigerous cysts sometimes show areas of mucous metaplasia within their stratified squamous epithelial lining. Approximately half of all central mucoepidermoid carcinomas show a coexistent odontogenic epithelial lining from which tumor transformation is demonstrable. An odontogenic cyst with extensive mucous cell metaplasia and the glandular or sialo-odontogenic cyst share many histologic features with low-grade central mucoepidermoid carcinoma, often making the diagnosis difficult.

TREATMENT

The management of mucoepidermoid carcinoma must be tailored to the type of tumor, its location, and grade of malignancy. It is noteworthy that low-grade mucoepidermoid carcinoma of the major salivary glands has a greater propensity to metastasize to the regional lymph nodes than similarly low-grade tumors of the minor salivary glands. Distant hematogenous metastasis of low-grade tumors is extremely rare. Conversely, high-grade tumors (regardless of the site of origin) are aggressive, with recurrences approaching 75%. Local metastasis to regional nodes and distant hematogenous metastasis to the lungs, brain, and skeleton occur. The initial 5-year survival rate for high-grade tumors is over 70%; however, it drops to below 50% at 10 years and to 33% at 15 years. Death attributed to low-grade tumors is unusual.

In the parotid gland, treatment of mucoepidermoid tumors is lobectomy with cervical node dissection when regional nodes are palpable. For high-grade tumors, regional node dissection in the absence of detectable disease has been advocated (elective neck dissection). Postoperative radiotherapy is often advocated for high-grade tumors, and it may control tumors that cannot be adequately removed surgically. In the palate, low-grade tumors can be treated by wide local excision to include palatal bone, whereas high-grade carcinomas require more radical procedures such as palatotomy or partial maxillectomy. Of all intraoral sites the tongue carries the worst prognosis for mucoepidermoid carcinoma. Hemiglossectomy is indicated in addition to neck node dissection. Central tumors of the jaws, which are usually low grade, should be treated by en bloc resection, ensuring tumor-free margins of bone.

ADENOID CYSTIC CARCINOMA

ADENOID CYSTIC CARCINOMA: A malignant salivary gland tumor composed of cuboidal cells in a solid, cribriform ("Swiss cheese") or tubular pattern with a predilection for invading perineural lymphatic spaces.

Adenoid cystic carcinoma is a malignant salivary tumor that may arise in either major or minor salivary glands. Because of its frequent microscopic appearance

resembling cross-sections of tubular structures (cylinders), it was previously referred to as "cylindroma." The individual tumor cells resemble the intercalated ducts of normal glands. This tumor is prone to recur after surgery. Although the 5-year survival rate is quite good, long-term follow-up discloses a low cure rate with recurrences appearing 10 to 15 years after initial treatment.

CLINICAL FEATURES

Although adenoid cystic carcinoma may occur in persons of any age, the peak incidence is in the sixth decade of life with a slight female predilection. It is rare in children. Clinically, adenoid cystic carcinoma is most common in the parotid gland and is typically detectable as a subcutaneous mass anterior to or below the ear. Almost as many cases arise in the submandibular gland as in the parotid gland. Adenoid cystic carcinoma of the submandibular gland may become quite large before the patient notices its presence. Despite its malignant nature, its growth rate is slow. Over time the mass becomes indurated and fixed. Because it has a marked propensity to surround nerve trunks, when in the parotid gland, involvement of the facial nerve is quite common. Involvement of the facial nerve is clinically apparent as weakness of facial muscles or paralysis. Although minor salivary gland tumors occur nearly as often as parotid and submandibular gland tumors, the most common intraoral site is the palate (Figure 10-31). The minor salivary glands of the tongue, buccal mucosa, lips, and floor

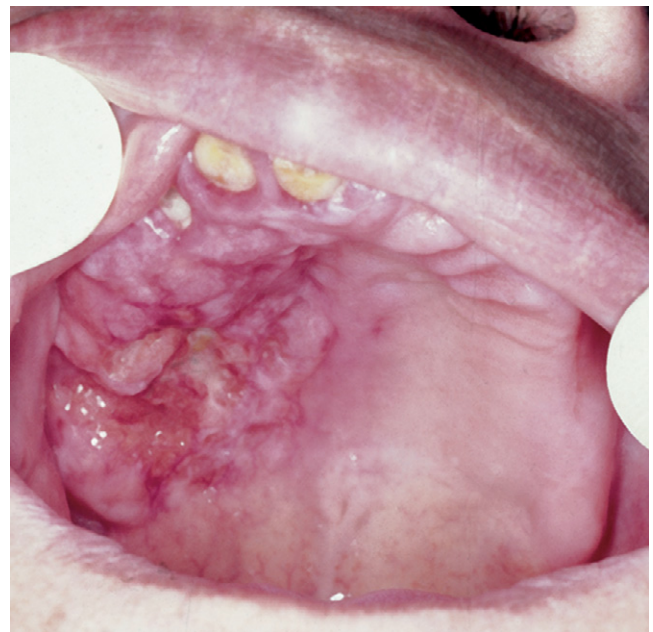


FIGURE 10-31
Adenoid cystic carcinoma. Diffuse large ulcerated lesion of the right palate.

of the mouth may also give rise to this tumor. In the palate, adenoid cystic carcinoma appears as an eccentric nodule that is usually ulcerated. There may be some palatal paresthesia because of involvement of the greater palatine branch of the trigeminal nerve.

HISTOPATHOLOGY

Most adenoid cystic carcinomas show classic microscopic patterns that allow for a straightforward diagnosis. However, the polymorphous low-grade adenocarcinoma shares many features with adenoid cystic carcinoma; occasionally a distinction between the two is problematic. The typical adenoid cystic carcinoma is composed of oval nests of cuboidal or polygonal epithelial cells with hyperchromatic nuclei. Mitotic figures are rare. Three patterns of growth exist, all of which may be encountered in a single tumor, although one pattern usually predominates. The first, the cribriform pattern, is classic (Figure 10-32). The tumor islands are punctuated with multiple prominent microcystic spaces that divide the lobules into numerous cylinders yielding a “Swiss cheese” or “honeycomb” appearance. These cylindric spaces contain either eosinophilic or basophilic secretion products that react positively with mucin stains. The cells oriented around the microcysts are not well polarized into true ductal cells. The stroma is mature and often hyalinized. The second, or tubular pattern, may dominate the tumor, showing only a few foci of cribriform elements. Small ductal elements prevail and are usually lined by one to three layers of basaloid cells. These tubuloductal formations are identified in both cross and longitudinal arrays with an intervening hyalinized stroma. The third, or **basaloid pattern**, consists of solid nests of basal cells that resemble those

seen in basal cell carcinoma or basal cell adenoma. The nuclei, however, show evidence of atypia, including hyperchromatism, pleomorphism, and increased mitotic activity. Most basaloid cylindromas will contain foci of cribriform or tubular configurations. Immunomarkers disclose the presence of cytokeratins and muscle-specific actin, indicating both ductal and myoepithelial differentiation. Common to all forms of adenoid cystic carcinoma is the tendency for perineural invasion. Tubular concentric laminations of tumor cells wrap themselves around the perineurium of nerve cells (Figure 10-33), where they have actually invaded the perineural lymphatic vessels. This neurotropism is characteristic yet not pathognomonic. It accounts for the high local recurrence seen after surgery, because tumor cells may spread along nerve trunks for a considerable distance from the main tumor mass.

TREATMENT

Adenoid cystic carcinoma is a slow-growing adenocarcinoma with a tendency for neural involvement, a phenomenon that contributes greatly to its ability to recur many years after the initial surgery. Commonly, the 5-year survival rate is good; however, recurrences are common after 10 to 15 years. A tendency for both regional and hematogenous tumor spread exists, and nearly 40% of the patients develop metastasis.

Distant spread to the lungs and bone is more common than nodal disease. Even so, the most troublesome consequence of adenoid cystic carcinoma is its persistence and tendency to recur locally (Figure 10-34). In the major glands, total sialoadenectomy is the treatment of choice and frozen section samples of the surrounding neural bundles should be evaluated at the

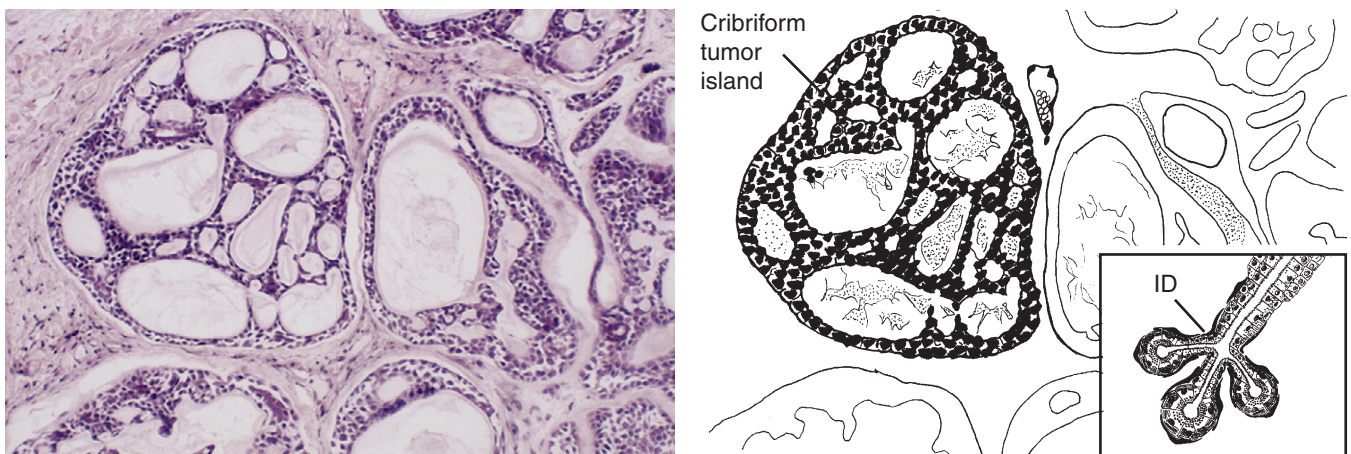
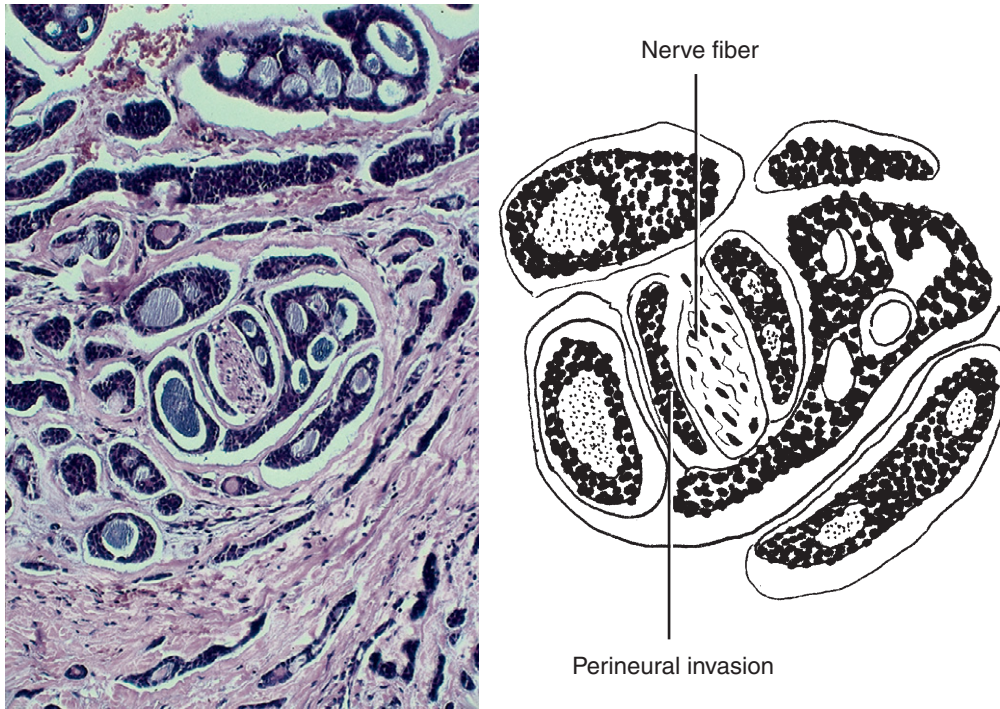
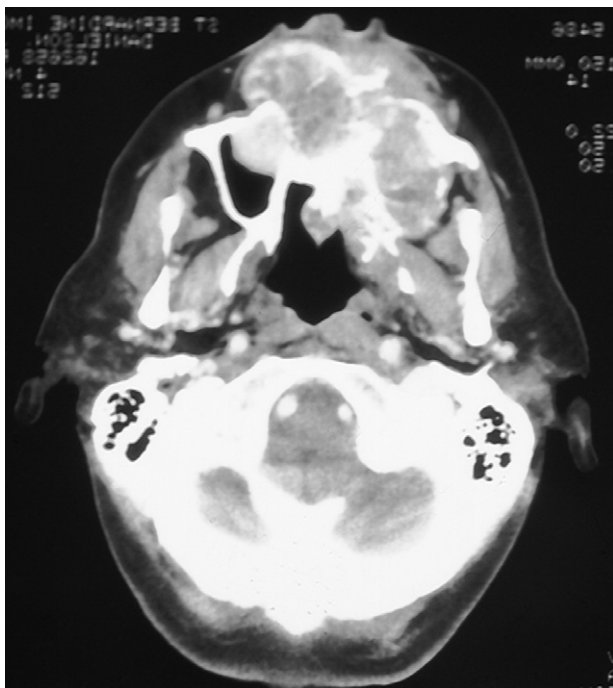


FIGURE 10-32

Adenoid cystic carcinoma. Cribriform pattern with a “Swiss cheese” appearance.
ID, Intercalated duct cells.

**FIGURE 10-33**

Adenoid cystic carcinoma. Affinity for perineural invasion by tumor cells (neurotropism) is evident.

**FIGURE 10-34**

Recurrent adenoid cystic carcinoma. Computed tomography axial image shows extensive involvement of the anterior maxilla and antrum (top right area).

time of surgery for the presence of perineural invasion. Involved nerves must be evaluated until tumor cells are no longer identifiable. Palatal adenoid cystic carcinomas may extend into the pterygomaxillary space via the greater palatine nerve. Partial maxillectomy is the treatment of choice. Lymph node metastasis at the time of initial diagnosis is usually not common; when detectable clinically or with special imaging techniques, node dissection may be indicated. Postoperative radiation therapy is usually advocated, because the tumor is radiosensitive and any remaining undetected tumor foci may be eliminated in this manner.

ACINIC CELL CARCINOMA

ACINIC CELL CARCINOMA: A malignant salivary gland tumor primarily of the parotid gland and composed of pale-staining acinar cells usually in a solid or follicular pattern with little visible stroma.

Acinic cell carcinoma is usually found in the parotid gland and is uncommon in the other major and minor salivary glands. After mucoepidermoid carcinoma, it is the second most common malignant salivary gland tumor of the parotid gland. The tumor cells consist of either serous or mucous acinar cells with few

ductal or myoepithelial cell elements. The tumor is a low-grade malignancy with slow growth potential; however, like adenoid cystic carcinoma, a tendency for local recurrence exists long after initial therapy.

CLINICAL FEATURES

The parotid gland is the site of origin in over 80% of acinic cell carcinomas, and intraoral localization is encountered in 15% (Figure 10-35). Unlike most oral salivary tumors that tend to occur in the palate, the few tumors that arise from oral minor glands are most often located in the buccal mucosa and lips. Women are affected more frequently than men, and no age predilection exists. The tumor occurs with equal frequency in patients throughout the second to seventh decades; rare cases are seen in young children. Most acinic cell carcinomas are well demarcated and movable. In the parotid gland some may feel fluctuant, because cystic spaces can occasionally be present. The overlying skin or mucosa is intact. At the time of initial examination most tumors are smaller than 3 cm in diameter and rarely exhibit facial nerve compression and paralysis. In the lip and buccal

mucosa, a firm and well-defined submucosal mass is detected, either visually or by palpation.

HISTOPATHOLOGY

The cells of acinic cell carcinoma resemble the secretory units of salivary tissue and may be mucous, serous, or seromucous. Microscopy shows that the individual cells are usually rich in cytoplasm and the contents stain lightly basophilic or amphophilic. In the common forms of acinic cell carcinoma, zymogen granules are rare. In the unusual zymogen-secreting tumors, the acinar cell components are stippled with richly basophilic granules. Most acinic cell neoplasms elaborate a more seromucous material, which is not granular. The mucosubstances stain with periodic acid-Schiff (PAS) and are diastase resistant, indicating that they do not contain large amounts of glycogen.

These acinar cells are arranged in a variety of growth patterns, which can be described as solid, microcystic, papillary cystic, and follicular (Figure 10-36). These patterns have no prognostic significance. In the solid



FIGURE 10-35
Acinic cell carcinoma. Smooth, nonulcerated lesion of minor salivary gland located on the buccal mucosa.

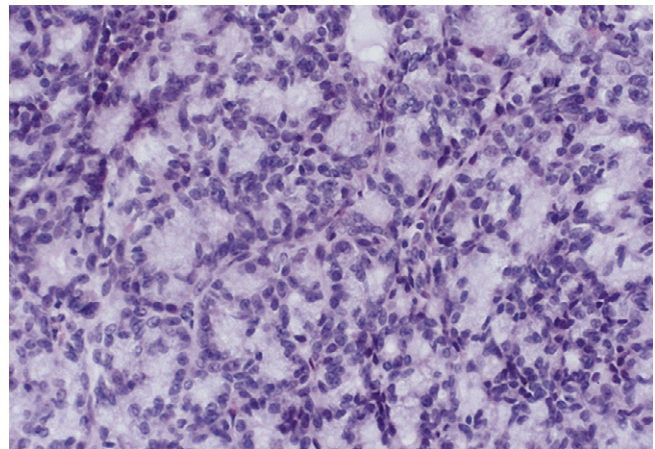


FIGURE 10-36
Acinic cell carcinoma. Sheets and clusters of neoplastic acinar cells with little supportive connective tissue stroma. A, Acinar cell.

type, fine capillary septa divide sheets of acinar cells into indistinct lobules. This same pattern is encountered in the microcystic variant, except that varying sizes of microcysts are scattered throughout. In the papillary cystic form, large cystic spaces are seen and large papillary fronds of solid and microcystic acinar configurations protrude into the cystic spaces. A characteristic finding in microcystic and papillary cystic foci are acinar cells that appear to be beaded or yield a hobnail pattern when they line a cystic space. The stroma of acinar cell carcinoma is very scant. The outer margin of the tumor is lobulated, relatively well demarcated, and sometimes may actually be partially encapsulated. Lymphoid tissue with germinal centers is commonly encountered around the periphery and may represent residual parotid lymphoid tissue or a lymphoid reaction to the tumor itself.

TREATMENT

In the short term, acinar cell carcinoma masquerades as a benign tumor, because very few problems are encountered in the first few years after surgical excision. Long-term follow-up, however, discloses that 30% may recur and 15% will metastasize. The 5-year survival rate after surgery is over 80% but drops to less than 65% at 10 years. Tumors located in the superficial lobes of the parotid gland may be treated by lobectomy, whereas total parotidectomy is advocated for deep lobe neoplasms. Neck dissection is indicated only when the clinician finds evidence of regional metastasis. The tumor is radioresistant.

POLYMORPHOUS LOW-GRADE ADENOCARCINOMA

POLYMORPHOUS LOW-GRADE ADENOCARCINOMA:

A malignant salivary gland tumor with a predilection for the minor glands that is composed of a wide variety of lobular and cribriform patterns in the central areas, laminated single-file tubular patterns in the periphery, and has a low potential for metastasis.

Polymorphous low-grade adenocarcinoma generally occurs in the minor salivary glands of the oral cavity and only rarely arises within the major salivary glands. Some adenocarcinomas arising in preexisting PA (carcinoma ex pleomorphic adenoma) will show growth patterns strikingly similar or identical to polymorphous low-grade adenocarcinoma. The population of tumor cells is quite varied, with many growth patterns encountered; hence the term *polymorphous*. Most of the cells resemble the intercalated or terminal salivary ducts. Confusion with adenoid cystic carcinoma may occur in some cases, because both tumors have some common cellular configurations that can be seen microscopically.

CLINICAL FEATURES

A significant female predilection exists for polymorphous low-grade adenocarcinoma. Most tumors are found in patients who are in the sixth to eighth decades. At present, none has been found in patients in the first 2 decades of life. The tumor occurs in the palate 60% of the time, 35% are found in the lips and buccal mucosa, and only a few tumors are found in other oral mucosal sites (Figure 10-37). They are painless masses, firm on palpation, and fixed when in the palate. Surface ulceration is rarely seen. A history of slow growth exists, and most tumors are smaller than 3 cm in diameter.

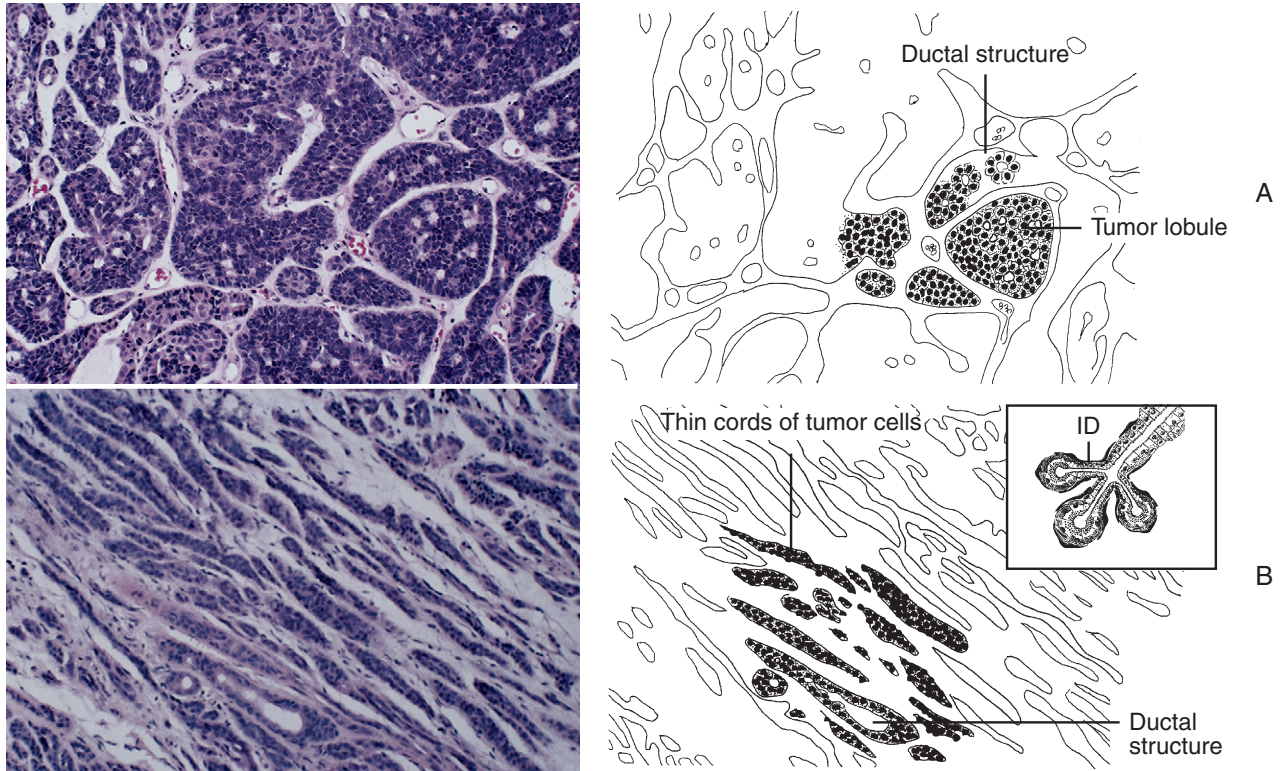
HISTOPATHOLOGY

Confusion with adenoid cystic carcinoma based on microscopically viewed features can be problematic; however, most polymorphous low-grade adenocarcinomas have distinctly different growth patterns. The tumor is usually well demarcated but is not encapsulated. Invasive tumor nests are generally seen around the periphery with extension into adjacent minor salivary gland lobules or muscle fibers, depending on the location. Two basic growth patterns are encountered: lobular and cribriform (Figure 10-38, A). The *lobular pattern* is composed of ovoid or round nests of basaloid cells with monomorphic nuclei; the connective tissue stroma is scant and mature. The *cribriform pattern* is similar to that of adenoid cystic carcinoma; it has a “Swiss cheese” appearance, because the tumor lobules are riddled with multiple microcysts. Perhaps the most distinguishing feature of polymorphous low-grade adenocarcinoma is found around the periphery of the lesion. In this region the tumor cells are arranged in parallel arrays of elongated, single-file tubular formations (Figure 10-38, B). These single-file tubular structures appear to be stacked upon one another, producing an



FIGURE 10-37

Polymorphous low-grade adenocarcinoma. Large, nodular ulcerated lesion involving the palate and the alveolar bone.

**FIGURE 10-38**

Polymorphous low-grade adenocarcinoma. **A**, Lobular pattern of basaloid tumor cells with lumen formation. **B**, Parallel tubular structures (*thin cords*) found at periphery of the lesion. *ID*, Intercalated duct cells.

“onionskin” or laminated appearance. The nuclei are large, yet uniform, and the nucleoplasm is granular or stippled. Perineural invasion may also be seen and is therefore not a reliable feature in differentiating this tumor from adenoid cystic carcinoma.

TREATMENT

Polymorphous low-grade adenocarcinoma, as the name indicates, is a low-grade, indolent malignancy. At present, only a single death has been reported from a local recurrence. Recurrences are commonly the result of incomplete excision. Distant hematogenous metastases do not occur. Only 5% have been reported to spread locally. Surgical excision including wide margins is the treatment of choice. Any identifiable nerve fibers passing into the tumor should be surgically tracked, and frozen section samples should be evaluated. In the palate a partial maxillectomy is recommended.

OTHER ADENOCARCINOMAS

A variety of less commonly encountered malignant tumors of salivary epithelia exists. These tumors are diagnosed microscopically based on histopathologic pat-

terns of differentiation and growth characteristics. When no specific features distinguish these tumors from other well-defined entities, they are referred to as *adenocarcinoma, not otherwise specified (NOS)*.

CLINICAL FEATURES

The various types of adenocarcinomas of salivary origin are usually indurated tumors that, when large, are fixed to the surrounding tissues. In the oral cavity they arise from the accessory salivary glands and may be encountered anywhere in the upper air passages where salivary glandular tissue is found, including the nasal cavity, sinuses, and larynx. These tumors of the minor salivary gland are indurated and often exhibit surface telangiectasia and ulceration. Being malignant, these tumors have potential for nodal and distant metastases. The degree of this potential can be correlated with the histopathology, some being slow to spread and others rapidly progressive with a poor prognosis.

HISTOPATHOLOGY

Adenocarcinoma NOS is an infiltrative tumor with ductal structures showing cuboidal cells surrounding lumina. In other areas of the tumor, ductlike cords or

solid nests are found. Salivary duct carcinoma is characterized by large round to oval islands of tumor cells with microcystic spaces arranged in a cribriform pattern. The individual cells show marked pleomorphism and atypical mitotic figures; this degree of cytologic atypia is unique and not encountered in most of the other types of adenocarcinomas.

The epithelial-myoeplithelial carcinoma of intercalated ducts is characterized by small, intercalated, duct-like structures with a surrounding outer layer of clear cells; the stroma is often hyalinized because of thickened basement membranes surrounding the ductal structures. However, other salivary malignancies are comprised of clear cells arranged in sheets and nests with a scant fibrous stroma (clear cell carcinoma of salivary origin). Basal cell adenocarcinoma resembles the basal cell adenoma, in that it is comprised of oval nests of monomorphic basaloid cells with some areas differentiating into small ductal structures. The tumor lacks encapsulation, showing invasion of adjacent glandular tissue. Other rare malignancies of the salivary glands include *mucinous adenocarcinoma*, *small and large cell neuroendocrine carcinoma*, *squamous cell carcinoma of salivary origin*, *carcinosarcoma*, and other *sarcomas* arising from the salivary stromal connective tissues. *MALT lymphoma* of salivary tissue is discussed in Chapter 12.

TREATMENT

Adenocarcinoma NOS and salivary duct carcinoma are aggressive malignancies with a high propensity for both nodal and distant metastases. Treatment consists of total sialectomy in the major glands and wide resection in minor gland tumors. The basal cell adenocarcinoma and epithelial-myoeplithelial carcinoma also require wide excision; yet both lesions are considered low-grade malignancies in which metastases are seen in less than 25% of the cases.

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CHAPTER OUTLINE

PHYSICAL INJURIES

- Teeth
 - Attrition
 - Abrasion
 - Erosion
 - Fracture
 - Avulsion
 - Internal Resorption
 - External Resorption
 - Ankylosis
- Gingiva
 - Toothbrush Trauma
 - Toothpick Injury
- Tongue
 - Traumatic Atrophic Glossitis
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 - Hairy Tongue
 - Fissured Tongue
 - Chronic Ulcers
- Mucosal Tissue
 - Factitious Injuries
 - Denture Injuries
 - Electrical Burns
 - Thermal Burns
- Radiation Injuries
 - Radiation Mucositis
 - Xerostomia
 - Radiation Caries
 - Osteoradionecrosis
 - Soft Tissue Radiation Injuries

CHEMICAL INJURIES

- Teeth
 - Tetracycline
 - Congenital Porphyria
 - Biliary Atresia
 - Erythroblastosis Fetalis
- Gingiva
 - Phenytoin
 - Cyclosporine
 - Nifedipine
- Mucosal Tissue
 - Amalgam
 - Graphite
- Chemical Burns
 - Acetylsalicylic Acid
 - Other Medications

ADDITIONAL KEY TERMS

- Bruxism
- Cemental tear
- Crown fractures
- Gilles de la Tourette syndrome
- Root fractures
- Stomatitis areata migrans
- Submerged (retained) deciduous molar
- Traumatic ulcerative granuloma with stromal eosinophilia



PHYSICAL INJURIES

TEETH

Physical injuries are among the most common causes of tooth defects. Most of the injuries are self-induced or factitious. Although some of these are purposeful because of a neurosis, psychosis, or hereditary condition, most are inadvertent. Injuries as the result of overzealous daily habits are the most common, with abuse of oral hygiene practices being most notable. On occasion, environmental elements such as toxic levels of chemicals in the air contribute to the loss of tooth structure in light of normal hygiene practices. The physical injuries of teeth have been divided into three major categories: (1) attrition, (2) abrasion, and (3) erosion.

Attrition

ATTRITION: *Loss of tooth structure because of the mechanical action of mastication.*

Some degree of attrition is normal, because it occurs naturally as an accumulative process over many years. It is normally present on the cuspal and incisal edges of the anterior teeth (Figure 11-1) and on the tips of the cusps of molars that are in occlusion. These changes become more pronounced with advanced age. Attrition is excessive and premature on the teeth of patients who habitually clench and grind their teeth (**bruxism**). The pattern of attrition will vary among these patients, depending on the interocclusal contacts and the relationship of the arches. In patients



FIGURE 11-1

Attrition. Anterior lower teeth exhibit extensive wear on the incisal edges, exposing the underlying sclerotic dentin.

with class II relationships the excessive wear tends to be on the molars, with the occlusal surfaces becoming nearly flat. Patients with class III relationships exhibit most of the wear on the incisal edges of the anterior teeth.

In some societies, greater attrition exists as the result of dietary habits. This was particularly evident in past and primitive societies in which diets that were more fibrous and in which abrasive particles became intermingled in the food during preparation. Excessive wear is still found in some cultures today, where day-long chewing of certain substances such as betel nuts is a common custom.

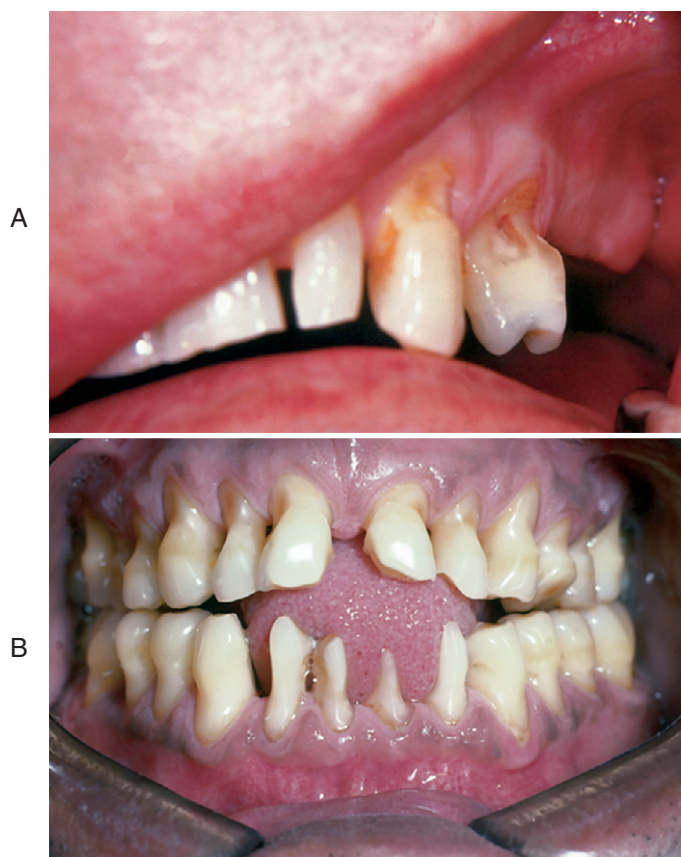
Because attrition is generally a slowly progressive process, the dentin and pulp tissue have time to react to the loss of tooth tissue. The exposed dentin undergoes sclerosis of the dentinal tubules while the pulp deposits layers of calcified tissue, referred to as *tertiary* or *reparative* dentin. This process protects the pulp from irritants that might otherwise permeate the dentin, thus it remains viable even in situations where more than half the crown has been lost because of attrition.

Abrasion

ABRASION: *Abnormal loss of tooth structure because of nonmasticatory physical friction.*

The most common cause of abrasion is overuse and misuse of the toothbrush (Figure 11-2, A) or the use of coarse abrasives while cleaning the teeth. In some cultures, teeth are cleaned with implements that are more abrasive than the bristle brushes and fine abrasives common in Western societies. In these societies the teeth commonly exhibit a characteristic pattern in which the buccal and labial surfaces exhibit excessive tooth loss, particularly of the cervical areas (Figure 11-2, B). Severe abrasion predominantly involves the anterior and premolar teeth of the arches, with the maxillary teeth more severely affected than the mandibular. In Western and other cultures the overuse of toothpicks to clean teeth or massage the gingiva often produces a distinctive pattern of interproximal wear. Linear patterns of tooth loss on the exposed cementum of older patients occur when dental floss is improperly used.

Other forms of nonhygienic habits will produce characteristic patterns of abrasion. Notching of the incisal edges of the anterior teeth is common when hairpins are constantly opened using the anterior teeth. A similar pattern of tooth loss involving several anterior teeth of the left or right anterior arches occurs in habitual pipe smokers.

**FIGURE 11-2**

Abrasion. **A**, Excessive and improper use of a toothbrush, producing notching on the buccal surfaces at the cervicoenamel junction of the cuspid and premolars. **B**, Extensive loss of tooth structures in a compulsive patient in whom the teeth were overzealously cleaned with a wooden instrument and a coarse abrasive.

Erosion

EROSION: A loss of tooth structure as the result of nonbacterial chemical causes.

The most common chemicals to contribute to erosive tooth loss are those with a pH in the acidic range. The continuous contact of the enamel with these chemicals leads to leaching of the calcifying salts and a reduction in its hardness. Tooth structure that has been weakened by this process is easily lost, even when normal hygiene techniques are used.

Most causes of erosions are known and can be attributed to an excessive diet of foods with an acid pH, such as citrus fruits and carbonated beverages (soft drinks). These foods produce a unique pattern of smooth saucer-shaped cavitations of the labial surfaces of the anterior teeth (Figure 11-3). Patients who

**FIGURE 11-3**

Erosion. The labial surfaces of the anterior teeth exhibit thinning of the enamel and rounding of the crowns with white opaque areas of demineralization common in patients with excessive intake of highly acidic foods and beverages.

suffer from regurgitation of acidic stomach contents develop erosions on the lingual surfaces of the teeth, particularly the anterior teeth. This occurs frequently during pregnancy and in patients suffering from bulimia (Figure 11-4). Other common causes of dental erosion are occupational. These are the result of the presence of certain atmospheric gases that become mixed with the saliva, producing acid solutions. These erosions are also located on the labial surfaces of the anterior teeth.

Fracture

Fractures of teeth occur under a wide variety of conditions. The most common are those associated with acute trauma, particularly in young patients. These are often caused by a fall or a sudden blow to the midface. Fractures may also occur during normal use of the teeth as the result of one or more of the following four predisposing factors: (1) the pulp has been rendered more brittle after it has become devitalized, (2) the presence of internal resorption, (3) the presence of large intra-coronal restorations (particularly mesial-occlusal-distal [MOD] fillings in premolars), and (4) teeth affected by dentinogenesis imperfecta or other congenital or acquired conditions that affect the integrity of the tooth structure.

The most commonly encountered tooth fractures are **crown fractures** of anterior teeth. These fractures have been classified as involving (1) enamel only; (2) enamel and dentin; and (3) enamel, dentin, and pulp. The most prevalent of these are the fractures

**FIGURE 11-4**

Bulimia. The lingual surfaces of the maxillary teeth show loss of enamel because of constant contact with regurgitated acidic stomach contents.

involving both enamel and dentin; most are oblique, involving one of the incisal corners. When dentin is exposed, bacterial invasion of the tubules and penetration into the pulp ensues unless the patient obtains prompt attention. Pain is usually associated with dentin exposure; however, when the pulp has been severed, pain may be absent. This severe pulpal trauma may not be reversible and usually requires immediate pulpal extirpation.

Root fractures represent a small percentage of the total number of tooth fractures. Most are of traumatic origin, occurring in patients between the ages of 10 and 20 years. The majority are horizontal fractures in the middle third of the root. The second most common root fracture occurs in the apical third of the root (Figure 11-5). Most teeth become nonvital immediately when root fracture occurs. Some root fractures may take other courses. They may heal by forming an inner layer of reparative dentin on the pulpal wall, or they may replace the hard tissue along the fracture line with granulation tissue that progresses to mature connective tissue. Others remain vital and proceed to round off the sharp fracture edges, separating the two fragments by connective tissue and bone. In some cases they may become nonvital with the fragments becoming surrounded by granulation tissue, which usually results in extensive resorption with eventual tooth loss. The chances of tooth resorption and loss are reduced if the tooth is immobilized for a time.

**FIGURE 11-5**

Root fracture. Fracture located at the junction of the middle and apical third of the root, with a small area of resorption occurring adjacent to the fracture line in the coronal portion of the tooth fragment.

A traumatic event is not always of sufficient force to fracture the tooth but is still capable of producing a **cemental tear**. Cemental tears are small fractures of the cementum, usually the result of sudden torsional (rotational) forces. These usually are not of clinical significance, because they seldom produce symptoms. They are occasionally observed as incidental findings during a histologic examination of periodontal tissue removed for other purposes.

Avulsion

AVULSION: The forceful displacement of a tooth in its socket.

Avulsion of teeth may be *partial or total*. A tooth becomes partially avulsed when it is moved but has not become devitalized. A totally avulsed tooth is one that has become nonvital because of extensive movement of the apex or it has been extruded from the socket, both of which result in severance of the apical blood supply. Avulsed teeth should be immediately repositioned and a determination made regarding their vitality.

Internal Resorption

INTERNAL RESORPTION: A form of tooth loss that begins within the pulpal chambers of intact teeth, destroying dentin as it extends outward in a uniform pattern toward the tooth surfaces.



FIGURE 11-6

Internal resorption. Clinical appearance of a tooth with a large area of internal resorption as revealed by a pink spot in the cervical third of the crown.



FIGURE 11-7

Internal resorption. Radiographic appearance of resorption that appears to be originating within the pulpal tissue of the root.

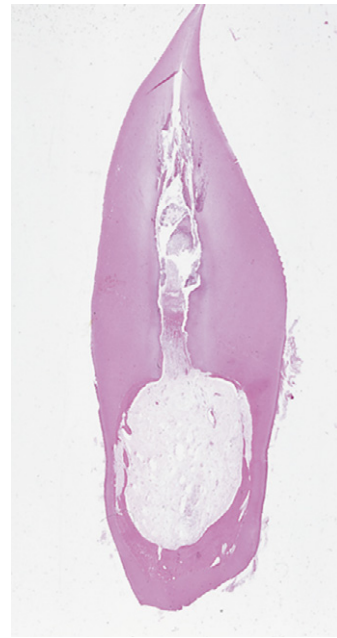


FIGURE 11-8

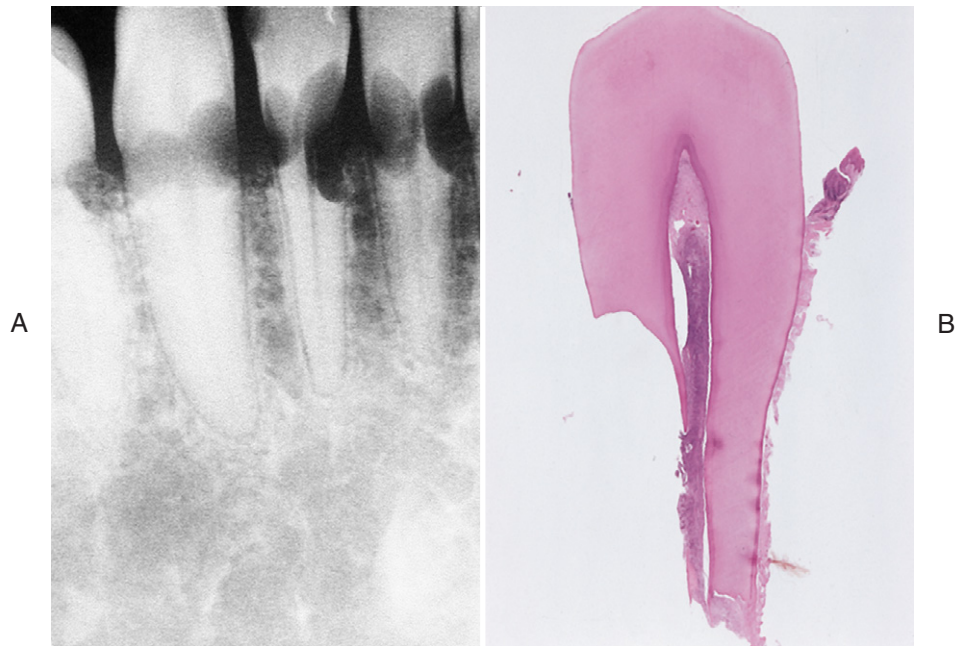
Internal resorption. Low-power microscopic appearance of an incisor containing characteristic vascular loose connective tissue within the area of root resorption.

Most occurrences of internal resorption are within the crown of anterior incisors and are idiopathic. The affected tooth is usually asymptomatic, with the lesion first detected by the appearance of a pink spot beneath the enamel surface (Figure 11-6). At this time, extensive loss of tooth structure has occurred, greatly weakening the tooth and predisposing it to fracture.

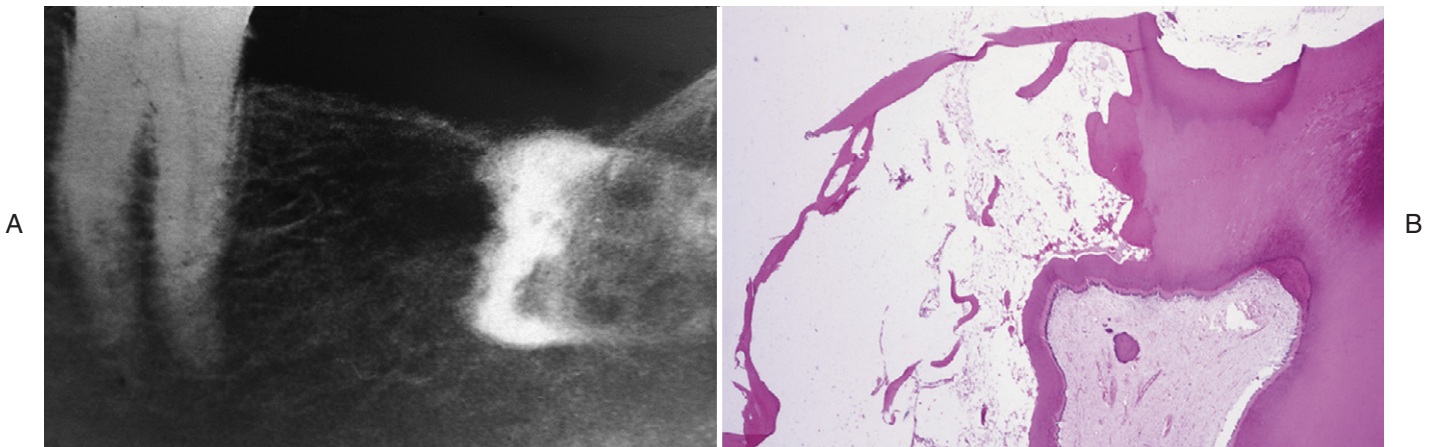
The radiographic appearance of internal resorption is distinctive. It usually consists of a fusiform enlargement of the pulpal chamber of one or more teeth that appears in either the crown or root pulpal chambers (Figure 11-7). In intact teeth histologic examination of the pulpal tissue in the area of the resorption reveals a loose connective tissue with increased vascularity and few inflammatory cells (Figure 11-8). When internal resorption is associated with caries exposure, pulpal treatments, or hairline fractures, the pulpal tissues will contain a granulation tissue that is densely infiltrated with acute and chronic inflammatory cells. If internal resorption has not progressed to the point of making the tooth structurally unsound, endodontic treatment can often halt the process.

External Resorption

EXTERNAL RESORPTION: A loss of tooth structure that begins on the outer surface and extends inward toward the pulp.

**FIGURE 11-9**

External resorption. **A**, Radiographic appearance of idiopathic external resorption involving the cervical area of multiple mandibular anterior teeth. **B**, Microscopic appearance of a decalcified tooth with an intact crown and external resorption of the middle and apical third of the root.

**FIGURE 11-10**

External resorption. **A**, Radiograph of an impacted tooth of long duration revealing mottling of crown and adjacent root. **B**, Microscopic appearance of a decalcified impacted molar with a large portion of the crown destroyed by external resorption. The pulpal tissue is unaffected by the process.

Several forms of external resorption exist. On an erupted tooth, lesions commonly begin in the cervical areas where they are usually considered idiopathic (Figure 11-9, A); when they occur in the midroot area (Figure 11-9, B), they are commonly the result of a trauma-

matic incident; and at the apex they commonly are the result of an encroaching inflammatory or neoplastic lesion. Impacted teeth of long duration can also undergo resorption. The resorption usually begins on the enamel of the crown (Figure 11-10), appearing as a mottled area

**FIGURE 11-11**

External resorption. Radiograph of anterior maxillary incisors with blunted apical areas indicative of previous period of active resorption. This form of resorption is commonly associated with prior orthodontic treatment, tumors, or cysts in the area.

with indistinct borders and progressing to the dentin. As with internal resorption, the process is without pain or other symptoms.

Evidence of external resorption of the root apices may be found in either a regional (Figure 11-11) or a generalized pattern throughout the mouth. These patterns are commonly the result of overly aggressive orthodontic movement of the teeth at an earlier time. In some patients apical resorption of multiple teeth is in an active state. This is commonly the result of a chronic form of excessive traumatic occlusion.

Transplanted and reimplanted teeth have a high incidence of developing external resorption. In the case of Reimplantation, it has been shown that the time between removal and subsequent reimplantation is of utmost importance in determining if the tooth will eventually be lost to postimplant external resorption.

Ankylosis

ANKYLOSIS: Fusion of the cementum or dentin to the surrounding alveolar bone after loss of the intervening periodontal membrane.

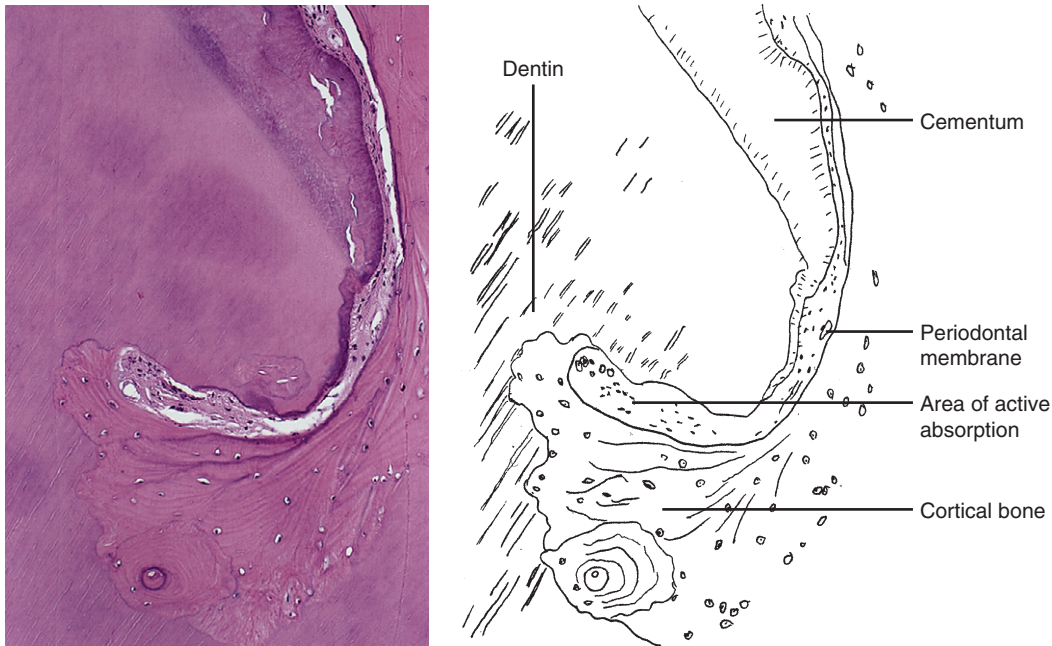
Within the dental arch, ankylosis most commonly involves the primary second molar; however, any tooth

may undergo this process after a traumatic incident. The exact pathogenesis of tooth ankylosis is unknown. It appears that whenever the connective tissue of the periodontal membrane is lost, it allows cementum, dentin, or both to come in direct contact with alveolar bone, resulting in fusion of these two opposing calcified structures (Figure 11-12). Ankylosis is also found when the normal physiologic resorption of the roots of deciduous teeth is interrupted or curtailed. When this occurs the granulation tissue surrounding the resorbing roots reverts to a fibrous tissue that goes on to become bone and fuses with the surrounding alveolar bone.

Another cause of ankylosis is chronic or acute trauma, either of which can cause inflammation and destruction of the periodontal membrane. Autoimplanted or reimplanted avulsed teeth in which the periodontal membrane has been destroyed usually undergo some degree of ankylosis if they are not lost by external resorption. In general, nearly any factor that can cause external root resorption has the potential to result in ankylosis. This includes rapid orthodontic movement, periapical infections, and occlusal traumatism. On rare occasions, long-standing impacted teeth will become ankylosed. Often the impacted tooth is not completely ankylosed but fused only in one or two areas.

The most common example of ankylosis is the **submerged (retained) deciduous molar**, usually located in the second mandibular premolar location (Figure 11-13). The submerged appearance occurs because the occlusal table of the retained smaller deciduous molar is located below the rest of the teeth in the arch. In many cases it is merely a deciduous tooth that has not yet undergone normal root resorption, allowing it to be shed in a timely manner. Eventually the surrounding earlier-erupting permanent teeth lock the submerged deciduous molar in its original position, and the primary molar that may have had some physiologic resorption often becomes ankylosed to the surrounding bone. In such situations if an underlying premolar is present, it will either remain impacted or will eventually erupt buccally or lingually in the arch, resulting in local malocclusion. Often the deciduous molar becomes locked in position because of a congenital absence of an underlying permanent premolar, resulting in a lack of stimulation for root resorption.

Making an accurate assessment that a tooth may be ankylosed is of utmost importance when extraction by luxation is contemplated. Failure to do so usually results in root breakage and the possibility of fracture of the surrounding alveolar bone. The most effective aid to diagnosis is the availability of periapical radiographs that demonstrate the presence or absence of a uniform periodontal space.

**FIGURE 11-12**

Ankylosis. Photomicrograph of partially ankylosed tooth illustrating an area with an absence of ankylosis, with root dentin (*left*) containing cementum and a periodontal membrane in the coronal portion of the root. An area of ankylosis is also evident in the apical portion in which the root dentin is fused to mature alveolar bone (*right*) in the absence of a cementum layer and periodontal membrane. At the junction of the two (*center*), a zone of active external resorption is present.

**FIGURE 11-13**

Submerged tooth. Radiograph of a retained deciduous second molar with its occlusal surface beneath the occlusal plane of the surrounding teeth.

**FIGURE 11-14**

Toothbrush trauma. Areas of erosion and acute inflammation are present, typically located on the marginal gingiva in the cuspid and premolar areas.

GINGIVA

Toothbrush Trauma

Lesions of the marginal and attached gingiva created by the chronic physical irritation of toothbrush bristles are usually confused with a number of other disease

processes. They may appear as white, red, or ulcerative lesions. Although any area of a quadrant can be involved, the lesions are most commonly present on the maxillary gingiva over the premolars and cuspids, because these are the locations that maximal pressure can be exerted during brushing (Figure 11-14). Lesions will



FIGURE 11-15
Toothbrush trauma. Chronic toothbrush abuse illustrating permanent loss of soft tissue, underlying bone, and tooth structure.

be more severe on the left if the patient is right handed and vice versa.

The injury commonly appears as linear superficial erosions against a red background. These lesions are easily confused with several of the vesiculoulcerative and infectious diseases; misdiagnosis and unsuccessful treatment are common problems.

When more severe forms of toothbrush injury occur, the lesions appear as deep clefts of the gingival margin, with generalized severe gingival recession and deep horizontal notching of the dentin of the exposed root surfaces. In severe cases the underlying alveolar bone will be lost and does not return when the destructive traumatic activity is reversed even though much of the gingival damage to the soft tissue improves (Figure 11-15).

Diagnosis often requires a tissue biopsy to rule out other disease processes. The histologic features of toothbrush injury are similar to those of a superficial ulcer caused by excess pressure or other nonspecific causes. They consist of a focal loss of the overlying epithelium, a superficial zone of granulation tissue over fibrous tissue, and a diffuse infiltrate of lymphocytes and plasma cells. Adjacent to the ulcers, the epithelium exhibits mild hyperorthokeratosis and acanthosis. Treatment consists of identifying the cause as a mechanical loss of the gingiva and tooth structure and helping the patient recognize the factitious nature of the injuries and how maintenance of oral hygiene can be attained without injury to the soft tissues.

Toothpick Injury

Toothpick injury of the gingiva is closely related to the previously discussed toothbrush injury. It is also the result of habitual, overzealous use of a common utensil for oral hygiene. The clinical appearance of toothpick injury is different, because usually only one or two lesions are present. Lesions involve loss of soft and hard tissues. The interdental papilla in these areas is usually lost and replaced by a depression that includes both the buccal and lingual aspects of the gingiva. The injury to the tooth itself consists of loss of cementum, dentin, and cervical enamel on the mesial and distal portions of adjacent teeth.

TONGUE

Traumatic Atrophic Glossitis

TRAUMATIC ATROPHIC GLOSSITIS: *Focal sensitive erythematous areas of the tongue as the result of a habit in which the filiform papillae are lost, the fungiform papillae are enlarged and reddened, and the epithelium is thinned.*

The most common location for traumatic atrophic glossitis is the anterior tip of the tongue (Figure 11-16). Less commonly, lesions are located on the lateral margins, extending onto the dorsal surfaces. They are frequently found in patients who have had recent restorations or other changes in their oral environment. Patients with atrophic glossitis usually overuse their tongues in a compulsive manner to explore recently placed restorations or other intraoral changes such as broken fillings, chipped cusps, or sharp incisal edges. The lesions located on the lateral tongue occur secondary to the extensive

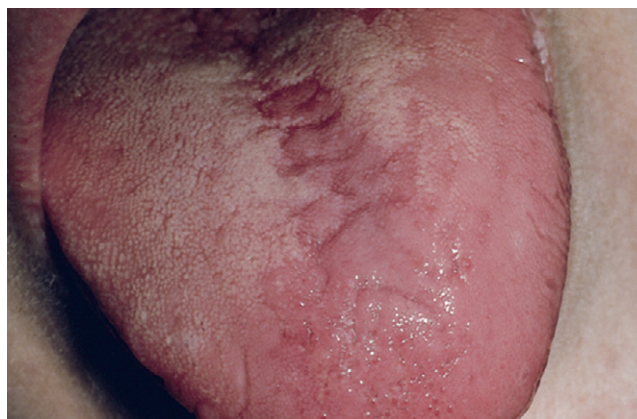


FIGURE 11-16
Traumatic atrophic glossitis. The tongue exhibits patchy loss of filiform papillae and erythema because of chronic excessive movement of the tongue. The tip of the tongue contains enlarged and reddened fungiform papillae.

movement of the anterior tongue over the crowns of the cuspids and premolars. Other causes of this condition are a loose upper denture that is constantly being resealed with the tongue, extensive calculus on the lingual surfaces of the mandibular teeth, and malaligned or crowded anterior teeth.

HISTOPATHOLOGY

The microscopic features of the lesions are those of a nonspecific inflammation of the mucosa (mucositis), which consists of thinned epithelium devoid of filiform papillae and connective tissue containing a diffuse infiltrate of lymphocytes and plasma cells, as well as dilated capillaries and venules. Treatment consists of identifying the factors that become the focus of the patient's attention and correcting them and any other rough or uncomfortable areas such as exposed margins, protrusions, sharp edges, calculus deposits, or loose appliances. To ensure continued oral comfort, the patient must be made aware of the necessity to curtail compulsive movements of the tongue.

Benign Migratory Glossitis

BENIGN MIGRATORY GLOSSITIS: *Multiple sensitive irregularly shaped erythematous patches of the tongue with arcuate white rims that enlarge and change shape daily.*

Benign migratory glossitis is also commonly referred to as *geographic tongue*, because the clinical appearance of the tongue often resembles a map of the world. The



FIGURE 11-17
Benign migratory glossitis. The tongue demonstrates the typical erythematous patches with a distinctive white rim on the dorsal surface. The tip exhibits features of atrophic glossitis.

cause of this lesion is still unknown; however, many feel that chronic irritation, similar to that described as the cause of chronic atrophic glossitis, is a significant contributing factor. Many patients will have crowding of the lower arch with one or more mandibular premolars or anterior incisors in linguoversion, producing some degree of irritation of the tongue even during normal movement. Periods of excessive tongue movement produce exacerbations of the condition.

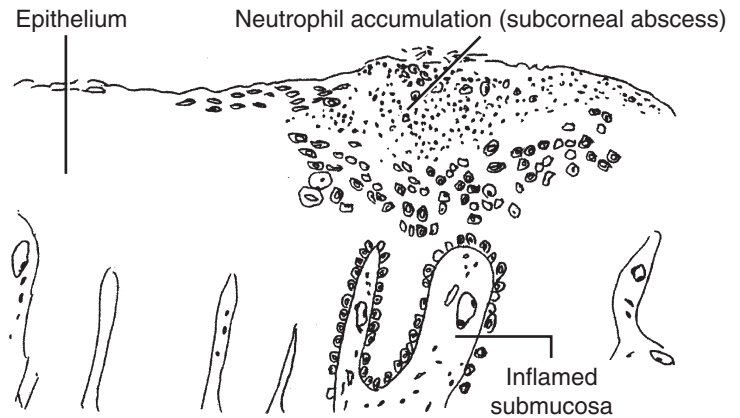
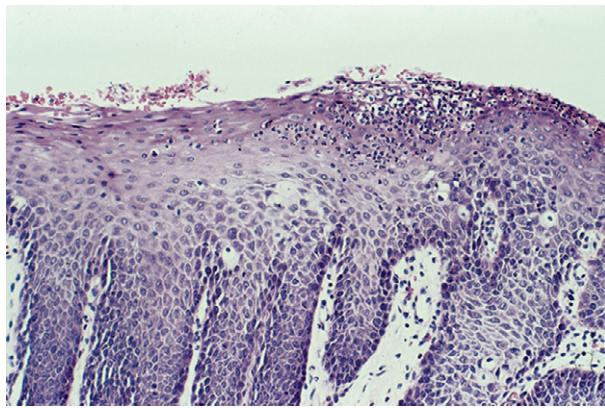
CLINICAL FEATURES

A distinctive clinical feature of benign migratory glossitis is the daily change in the size and shape of the lesions. Patients of all age groups have been found to exhibit these tongue lesions. New lesions commonly begin on the lateral borders and anterior tip of the tongue and gradually enlarge in a circumferential pattern. Individual lesions have a characteristic appearance consisting of a central atrophic area exhibiting loss of the filiform papillae. An erythematous zone with a slightly raised, distinct, whitish line at the junction with the normal tissue rims the atrophic areas (Figure 11-17). In ensuing days, the epithelium regenerates and the central area of the lesion gradually develops a normal appearance. As the lesion enlarges, its borders gradually become less distinct.

Similar-appearing lesions consisting of circular or arcuate lesions of other oral mucosal surfaces, such as the ventral tongue (Figure 11-18), floor of the mouth, and buccal vestibule, are occasionally present and referred to as **stomatitis areata migrans**. The clinical behavior of these lesions is similar to that of benign migratory glossitis, although no associated traumatic factors are usually apparent.



FIGURE 11-18
Stomatitis areata migrans. The ventral surface of the tongue exhibits arcuate raised lines against an erythematous background.

**FIGURE 11-19**

Benign migratory glossitis and stomatitis areata migrans. Microscopic features of both conditions are identical, consisting of a localized zone in the parakeratin layer with an accumulation of neutrophils (subcorneal abscess) that corresponds to the location of the distinctive arcuate white lines observed clinically.

HISTOPATHOLOGY

The microscopic appearances of benign migratory glossitis and stomatitis areata migrans are distinctive, consisting of an outer zone of subcorneal abscesses separating the normal from the atrophic epithelium. The underlying connective tissue contains an infiltrate of chronic inflammatory cells and an increase in the size and number of vascular structures (Figure 11-19).

TREATMENT

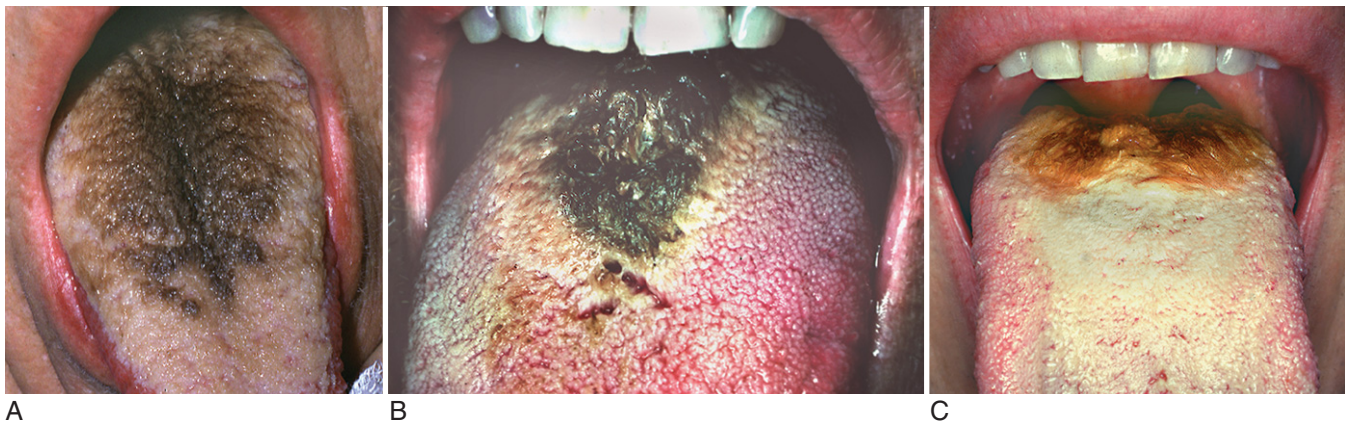
Treatment is empiric and consists of removing local sources of irritation and informing the patient of the factors and circumstances that may contribute to the

exacerbation of the disease. Brushing of the tongue should be avoided, because it tends to intensify and prolong the condition.

Hairy Tongue

HAIRY TONGUE: Abnormally elongated filiform papilla of the dorsal tongue that often become discolored from chromogenic bacteria or extrinsic substances.

Normally, the dorsal surface of the tongue is composed of fine, whitish, filiform papillae on a pink mucosal background. Occasionally, the filiform papillae

**FIGURE 11-20**

Hairy tongue. **A**, Generalized elongated filiform papillae with black coloration involving the posterior and middle thirds of tongue (black hairy tongue). **B**, Black hairy tongue confined to posterior third of tongue. **C**, Generalized hairy tongue with light-brown pigmentation of posterior third and yellow-cream coloration of the remaining dorsal tongue.

fail to shed their superficial layer of keratin, allowing it to accumulate and elongate the papillae into hairlike strands. The causes of the decrease in the normal pattern of desquamation are unknown but have been associated with a variety of factors such as smoking, chromogenic bacteria, medications, or foods.

The elongated papillae are generally confined to the posterior third of the dorsal tongue but may include the middle third in lesser amounts. In some patients the hairlike strands may become sufficiently elongated to tickle the uvula or soft palate or cause gagging. The elongated papillae may become matted and stained. Colors vary from black to cream, with most shades of brown (Figure 11-20). However, hairy tongue is more an annoying condition than a serious one. In milder cases, patients are usually concerned and uncomfortable with the appearance of the tongue, feeling that it portrays poor oral hygiene. They may seek a clinician's help to revert it to normal texture and color.

Treatment possibilities are limited. Attempts to eliminate possible contributing factors such as smoking, antibiotics, oxidizing mouthwashes containing peroxides and perborates, medications, and antacids (particularly those containing bismuth) meet with varying degrees of success. In some patients, lightly scraping or brushing the tongue daily aids the desquamation process and may reduce the severity of the condition. Commonly the condition spontaneously resolves. This has led some to theorize that the condition is caused by altered re-

gional bacterial flora that reverts back to the normal commensal organisms.

Fissured Tongue

FISSURED TONGUE: Multiple deep linear creases on a usually atrophic dorsal tongue of older patients and associated with multiple local and systemic conditions that may become symptomatic when secondarily infected.

Fissured tongue is a somewhat prevalent condition, particularly in older patients, and it appears to be more prominent in some families. It is commonly associated with other conditions, the most common being benign migratory glossitis (geographic tongue), chronic xerostomia, and the Melkersson-Rosenthal syndrome.

The fissures may be shallow or up to 5 to 6 mm deep, usually radiating laterally from the center in an angular pattern (Figure 11-21). The deeper fissures are subject to accumulation of food materials and bacteria that may produce an erythematous and sensitive tongue. In some patients the dorsal tongue may also be somewhat atrophic with a reduction in the filiform papillae. Unless the tongue becomes symptomatic or mouth odors develop, treatment usually is not indicated. Some relief may be obtained by gently removing food residue from deep fissures with a soft brush. Brushing the tongue when an associated benign migratory glossitis (geographic tongue) is present may worsen the latter condition.



FIGURE 11-21

Fissured tongue. **A**, Generalized deep fissures on an erythematous background and exhibiting a reduction in the filiform papillae and loss of normal whitish appearance. **B**, Combined fissured tongue and benign migratory glossitis (geographic tongue) of the lateral border (arrows). (Courtesy Dr. Russell E. Christensen.)

Management of an accompanying xerostomia and elimination of existing chronic tongue habits may provide some improvement. In most patients the condition remains unchanged for life.

Chronic Ulcers

Chronic tongue ulcers differ from ulcers in other parts of the mouth, because they tend to remain relatively unchanged for long periods. They are commonly found on the middle and posterior third of the lateral borders of the tongue, where each appears as a shallow ulceration surrounded by a raised rolled border of fibrous tissue and an outer wide zone of induration (Figure 11-22). These nonhealing indurated lesions are easily mistaken for squamous cell carcinomas, which commonly occur in the same area and can have a similar appearance.

Management of chronic tongue ulcers can be demanding, because identification of the irritating factors can be difficult. If a broken cusp, fractured restoration, or interfering denture clasp can be identified and corrected, healing may take place. In many cases, injury is the result of lack of tongue coordination during mastication caused by prescribed medication or a systemic condition such as Parkinson disease or a stroke that involves the cranial nerves. In other cases the tongue may be enlarged because of amyloidosis, acromegaly, hypothyroidism, hemangioma, lymphangioma, or allergic reactions. In some denture wearers, malpositioned posterior teeth on the denture base may be the contributing factor.



FIGURE 11-22
Chronic ulcer of the tongue. Deep ulcer located in the middle third of the lateral border of the tongue exhibits a raised indurated border resembling a malignant lesion.

It is not uncommon for an ulcer to remain unhealed even after correction of the predisposing factors. This is thought to occur because of the presence of the large and continually active tongue muscles that are close to the epithelial surface. The normal constant motion of the tongue prevents reepithelialization over the defect. In these cases surgical removal of the ulcer and its immediate surrounding fibrous tissue and the immobilization of the overlying epithelium by the use of ample numbers of sutures allow the defect to heal. The removed tissue also provides a specimen for microscopic evaluation to ensure the ulcer is not the result of a malignancy.

On occasion, chronic nonhealing ulcers of the tongue will have slightly different histopathologic features than ulcers in other areas. In these lesions, the granulation tissue and inflammatory reaction extends deeply into the underlying muscle. Distinguished by containing a disproportionate number of eosinophils, the lesions have been referred to as *traumatic ulcerative granuloma with stromal eosinophilia (TUGSE)*.

Other names for these unusual ulcers are *eosinophilic ulceration*, *traumatic granuloma*, and *eosinophilic granuloma of tongue*. When on the tip and ventral tongue of infants, it has been termed *Riga-Fede disease*. Similar lesions have been found on the buccal mucosa and other intraoral locations. In some lesions, nonmalignant atypical lymphocytes have been observed. Commonly, spontaneous healing occurs after biopsy to rule out squamous cell carcinoma.

MUCOSAL TISSUE

Factitious Injuries

Factitious injuries are inflicted by the patient. They may be consciously undertaken, the result of habit, or inadvertent. The most common are injuries incidental to toothbrushing, flossing, and the use of toothpicks, which were previously discussed.

Fingernail injuries to the oral tissue are among the most common of the factitious injuries. Patients often indicate that their habit was initiated and perpetuated because of itchiness in the area. On the gingiva, lesions are characteristic-appearing vertical clefts produced by forcing the free gingival margin apically. This habit results in root exposure on one or more teeth (Figure 11-23). In other accessible areas of the mucosa, the habit produces a chronic nonhealing ulcer (Figure 11-24).

Cheek and lip biting are also forms of habitual factitious injuries. The lesions have a characteristic shaggy appearance and are only present in areas where the mucosal soft tissue can be grasped between the patient's teeth. The usual pattern is along the occlusal line of the buccal mucosa and the labial surfaces of the lips (Figure 11-25).

In some emotionally disturbed patients, the secretive and purposeful production of oral lesions is performed

**FIGURE 11-23**

Factitious injury. Child exhibiting vertical clefting and reactive hyperplasia of fibrous tissue of the labial gingiva of the two maxillary anterior teeth as the result of habitual irritation with fingernail.

**FIGURE 11-25**

Factitious injury. Shaggy appearances of surface mucosa along the occlusal line and commissure area of the anterior buccal mucosa typical of chronic cheek biting.

**FIGURE 11-24**

Factitious injury. Adult with a chronic nonhealing ulcer of the anterior tonsillar pillar as the result of habitual scratching to relieve itchiness.

**FIGURE 11-26**

Factitious injury. Chronic self-mutilation of the anterior buccal vestibule with the fingernails in a patient with Gilles de la Tourette syndrome.

to obtain continuous attention and compassion from family and health care workers. The lesions are usually in the mandibular sulcus or on the lips. They may be produced with fingernails or instruments. Attempts to heal the areas are often fruitless, because patients usually interfere with the process to ensure failure.

Patients with **Gilles de la Tourette syndrome** are prone to spontaneous erratic behavior and incoherent facial expressions and verbalizations. Part of the syndrome is the tendency for self-mutilation, which is often directed to the oral tissue either through the use of the teeth or fingernails (Figure 11-26).

Denture Injuries

Denture injuries may be either acute or chronic. Acute injuries most commonly occur when a prosthetic appliance is new and not completely adjusted for fit and even distribution of occlusal forces. These appliances produce excessive pressure on one or more focal areas of the soft tissue, causing stasis or ischemia of the blood supply and severe frictional activity over the tissue, which results in ulceration and pain.

The chronic injuries are the result of gradual alteration in the supporting tissue while the denture base remains unchanged. In these situations the appliance becomes unstable and unevenly seated, leading to continuous mild frictional movements over the supporting tissue. The usual result is a large zone of reactive

tissue changes, the most notable occurring on the palate as an inflammatory papillary hyperplasia. It has also been referred to as *denture papillomatosis*. These lesions have a “raspberry” appearance, consisting of multiple small erythematous nodules (Figure 11-27). The area may become secondarily infected with *Candida albicans* and become symptomatic; patients experience a burning sensation of the palate. It is more common in patients who wear their dentures continuously.

Treatment consists of removing the appliances for prolonged periods, particularly at night, and using a tissue conditioner on the base of the denture. This is helpful in removing the inflammation and symptoms, particularly when used in combination with an antifungal agent. Unfortunately the condition seldom resolves completely, because the nodules are composed of dense fibrous tissue that does not return to normal. Some surgical intervention is often required before placement of the new prosthesis.

Over time as ridge support becomes diminished because of alveolar resorption, the denture flanges tend to gradually extend deeper in the sulcus, abnormally impinging on the soft tissue. In these areas a lesion is produced that is a combination of a chronic ulcer and a hyperplasia of the adjacent, chronically inflamed connective tissue (Figure 11-28, A). This lesion is referred to as *inflammatory fibrous hyperplasia* or commonly as *epulis fissuratum*. After correction of the denture the lesion will have some reduction in size and may even return to normal color, but usually a residual nodule or mass of fibrous tissue (Figure 11-28, B) remains that requires surgical removal.



FIGURE 11-27

Denture injury. Focal erythema and diffuse nodular hyperplasia under an ill-fitting partial denture.



FIGURE 11-28

Denture injury. **A**, Single large area of fibrous hyperplasia (epulis fissuratum) in the location of a long-term impingement of a denture flange on the anterior floor of the mouth. **B**, Low-power photomicrograph of denture-induced fibrous hyperplasia exhibiting a centrally located sulcus that corresponds to denture flange impingement.

Electrical Burns

Electrical burns most commonly occur in young children between the ages of 2 and 4 years. Most burns are the result of biting on the plugged cord of an appliance. The burns are produced by an arc that results from the electric current passing through the electrolyte-rich saliva. The arc reaches temperatures as high as 3000° C and is capable of quickly producing deep thermal burns and local tissue destruction. Less commonly, the damage occurs by sucking on the receptacle (female) end of an electrical extension cord. The severity of the injury depends on the voltage, amperage, and duration of the contact.

CLINICAL FEATURES

Clinically, electrical burns differ from thermal burns by having one or more deep craters with a light yellow base, each measuring 1 to 3 cm in diameter. Lesions are commonly painless and bloodless. Often large areas will feel cold, because normal-appearing tissue surrounding the crater is usually rendered ischemic. For 3 to 4 weeks the base of the crater and some of the surrounding tissue sloughs, leaving a large defect with ragged edges. The lower lip and angles of the mouth are most frequently involved. If untreated, patients may develop deformities that include microstomia, mucosa-to-alveolus adhesions, and morphologic alterations in the shape of the lips. If the alveolar ridges receive substantial current, development of the tooth buds in the area may be curtailed. Damage to the growth centers of bone results in failure of arch growth and shape that leads to malocclusion. Development of microstomia is of particular concern, because the patient is unable to maintain adequate oral hygiene and have routine restorative procedures performed.

HISTOPATHOLOGY

The histologic features of electrical arc burns consist of a large area of necrosis, protein coagulation, and fat liquefaction surrounded by a zone of granulation tissue and abundant inflammatory cells. If bone is involved, areas of necrotic bone containing empty lacunae and the production of sequestra are common.

TREATMENT

Treatment of the area is often temporarily delayed to allow time to determine the extent of the injury, because additional adjacent areas may not immediately appear to be severely damaged. Cosmetic reconstruction is often required in later years.

Thermal Burns

Most intraoral thermal burns are mild and result from contact with hot foods and beverages. The anterior tongue and palate are most frequently involved, be-

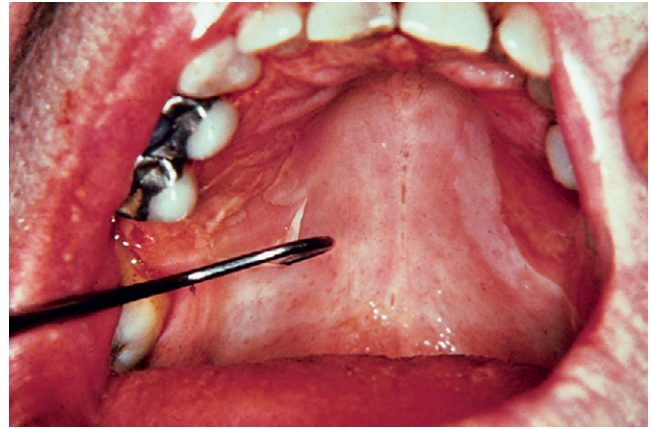


FIGURE 11-29

Thermal burn. Palate reveals erythema and superficial sloughing as the result of the ingestion of a hot beverage.

cause they are the first anatomic structures to be contacted. With mild burns the areas may exhibit slight erythema for a short period and resolve. In more severe burns, as sometimes occurs when hot cheese contacts the palate, the area exhibits sloughing of the superficial layers of epithelium, revealing an erythematous base that becomes sensitive for a much longer period (Figure 11-29). It is rare that permanent damage results from burns caused by hot foods of any type.

More serious thermal burns can occur during dental procedures when hot instruments accidentally contact tissue. These burns are frequently located on the lips and in the commissure areas, where they can cause a great deal of pain and heal with scar formation. Burns caused by overheated hydrocolloid impression material occur primarily on the gingiva and can be diffuse and painful. Healing is often slow with some permanent defects possible.

RADIATION INJURIES

Radiation injuries are the result of the ionizing effects of electromagnetic waves or energized particles on cells. Radiation therapy is commonly used in the management of head and neck malignancies. In the process of eliminating the diseased tissue, normal oral tissue in or near the same field is also damaged but usually to a lesser extent, allowing for the selective elimination of the neoplasm.

Therapeutic electromagnetic waves may be low energy, less than 1000 KeV (orthovoltage), or high energy, 4 million to 25 million KeV (supervoltage). The low-energy waves are effectively used for superficial skin or mucosal lesions, because energy absorption is

at the point of initial contact with tissue. When high energy is used, the maximal energy absorption is located substantially beneath the surface, resulting in a beneficial skin-sparing effect. This is a useful tool for the treatment of deep tumors or metastatic lesions in lymph nodes. Particulate radiation consists mostly of electrons, protons, neutrons, or heavily charged ions. The particulate energy is generated with a linear accelerator and is commonly in the 6 million to 21 million eV range.

The amount of cell damage depends on the amount of energy the tissue absorbs. This is measured as the radiation absorbed dose (*rad*) or as a gray (*Gy*). In these systems, 1 rad is equivalent to the absorption of 100 ergs/g and 1 Gy equals 100 rads. Cell necrosis can occur as a result of direct damage to the larger cell molecules or indirectly by means of the toxic compounds produced by the ionizing radiation when energy is absorbed. The indirect process occurs through the production of free radicals that combine to form toxic substances such as hydrogen peroxide. This mechanism can be manipulated therapeutically by superoxygenating tissue to increase the production of hydrogen peroxide and the cancericidal activity, allowing the use of lower doses. With particulate radiation, cell necrosis is primarily the result of direct damage rather than the production of free radicals.

Other factors determine the effectiveness of radiation. The stage of the cell cycle is important, because cells in G1/S and late G2 stages are very sensitive to radiation, whereas those in the other stages are relatively resistant. Because of this a single dose of radiation is effective only on a small number of cells; multiple exposures must be made as other cells go into their sensitive stages. Lesions containing cells that have a high index of mitotic activity, as occurs in the higher grades of malignancy, have more cells in the sensitive stages at any one time than the lower grades of malignancy and are usually more responsive to radiotherapy. Some lesions and tissues have little or no mitotic activity and are somewhat resistant to radiation. These are tissues such as nerve, muscle, bone, and mature cartilage. Other normal tissue contains cells that are as sensitive to radiation as the neoplastic cells that are being targeted, making it difficult to eliminate the lesion while sparing the surrounding tissue. These cells are lymphoblasts, bone marrow cells, germ cells of the ovaries and testes, and the epithelial cells of the mucosal lining of the stomach and intestines. In addition, some cells have a greater capacity to repair themselves, and others are able to quickly repopulate the void produced. Many of the negative factors are diminished when the total cancericidal dose is properly fractionated.

Radiation Mucositis

Because the basal cell layer of the mucosal epithelium normally has a somewhat high mitotic activity, it is especially sensitive to radiation that passes through it en route to a neoplastic lesion. During the second week of fractionated treatments, the exposed mucosa will initially become atrophic and erythematous. This phase quickly progresses to a layer of necrotic cells. The affected areas of the mucosa clinically appear pale yellow and when mechanically removed reveal an erythematous painful erosive area (Figure 11-30). In ensuing weeks many patients will develop superimposed bacterial and yeast (candidiasis) infections within the necrotic tissue, further increasing the degree of discomfort. By the end of the sixth week of treatment, particularly when large fields for treatment are used, the mucositis enlarges to include most of the oral cavity, nasopharynx, and esophagus. The mucositis persists at the same level of intensity for 2 additional weeks after the last treatment, and complete regeneration of normal epithelium occurs at the end of an additional month.

During all stages eating becomes progressively more painful and difficult as patients experience alteration or loss of taste and the saliva becomes thickened and



FIGURE 11-30

Radiation mucositis. The buccal mucosa exhibits an area of superficial white slough composed of necrotic epithelium against a background of erythematous atrophic mucosa.

stagnant. Symptoms are managed using frequent oral rinses with a solution of warm saline and baking soda. Often topical anesthetic is applied to allow the intake of food. Otherwise the patient is restricted to a liquid diet.

Xerostomia

When saliva production in the mouth is greatly reduced, the condition is referred to as *xerostomia*. It is a slowly evolving complication of radiation to the orofacial area, resulting from the damage to the parenchyma of the major and minor salivary glands in the path of the beam. Most radiation treatments intentionally include the lymph nodes, because they may contain metastatic lesions; the submandibular glands and lower lobes of the parotids are included in that field. Glands receiving less than the usual cancericidal dose of 6000 rads will receive less permanent damage. The parenchymal cells will have altered pH and electrolytes and reduced secretion of immunoglobulins. These alterations in the oral environment, particularly the loss of tissue immunoglobulins, alter the commensal relationships of the oral flora, allowing the normally present *C. albicans* to proliferate and become infective. The candidal infection contributes to the intensification of the pain and discomfort already present during the acute stages of radiation mucositis and leads to a chronic sore mouth that may last for months or years. Treatment with slowly dissolving lozenges containing antifungal agents such as clotrimazole is often effective in controlling the yeast infection. When medication is withdrawn, the condition often recurs until the saliva returns to normal.

Radiation Caries

No known deleterious effects on the teeth are directly the result of radiation. The dramatic increase in caries activity during radiation treatments is a result of a major shift of the pH of saliva into the acidic range and an accompanying reduction in its buffering capacity because of changes in the electrolytes. All teeth in the mouth are affected by the increased caries incidence, regardless of whether they are within the treatment field. Caries secondary to radiation have a distinctive pattern prevalent at the cemento-enamel junction (CEJ) of the buccolabial surfaces, locations normally resistant to caries (Figure 11-31). This pattern of caries often leads to amputation of the crowns if appropriate preventive measures are not implemented during the early stages of radiotherapy. The buccal and lingual smooth surfaces frequently develop white chalky or opaque areas because of the demineralization of enamel. These areas occur as a result of severe demineralization that takes place when the saliva becomes acidic and loses the mineral content that nor-



FIGURE 11-31

Radiation caries. Typical pattern of caries involvement after radiotherapy consisting of rampant caries circling the teeth at the cervical area and on the incisal edges. The teeth also exhibit a loss of translucency and appear whitish yellow and opaque. An acute candidiasis is evident on the soft tissue.

mally replenishes ions lost from the enamel surface. After several months of negative ion exchange, the surface softens, loses its translucency, and often crumbles, leaving shallow erosions and exposed softened dentin.

Management of the rampant caries and demineralization associated with radiotherapy require close monitoring by dental personnel. Oral hygiene must be meticulously maintained, and daily use of a fluoride gel is necessary.

Osteoradionecrosis

OSTEORADIONECROSIS: An acute form of osteomyelitis with sequestrum formation as a result of severe radiation damage to intraosseous blood vessels predisposing to areas of refractory infection and necrosis that is most commonly found in the mandible.

The effect of radiation on bone is usually secondary to the changes induced in the walls of the blood vessels that nourish it. Some direct damage by ionizing radiation on the osteocytes does occur when the dose is high enough and usually when the malignancy is in close proximity to bone. Because bone normally has minimal vascularity, particularly the bones of the mandible, it is subject to severe infections that are slow to resolve. Further compromise of the vascular flow because of radiation-induced endarteritis often results in an acute osteomyelitis that results in the sequestration of large pieces of nonvital bone (Figure 11-32). Bacterial organisms initially enter the damaged bone through portals created by extractions, periapical abscesses, periodontal disease, traumatic breaks in the tissue during general anesthetic or

surgical procedures, and the wearing of prosthetic appliances. Reducing these predisposing factors is of utmost importance in managing the oral cavity of patients receiving head and neck radiotherapy.

The management of osteoradionecrosis is difficult and often unsuccessful. Because the blood vessels are permanently damaged, it is difficult for nutrients and antibiotics to reach the bone and infectious microorganisms. Curettage of the necrotic tissues and attempts to obtain primary closure are often helpful. Otherwise the use of frequent lavage of the defect to promote epithelialization is the only hope to halt the process. Prevention of further opportunities for penetration of the microorganism into the bone is necessary to increase chances of success. When possible, teeth should be

restored or extracted; periodontal disease should be controlled before the initiation of radiotherapy. The use of fluoride gels and meticulous oral hygiene are necessary during and immediately after treatment to prevent the development of caries and periodontal disease.

Soft Tissue Radiation Injuries

The other oral soft tissues within the irradiated field will also incur some degree of damage. First to appear is a gradual loss in taste sensation that increases as treatments continue. This complication is particularly distressing to patients, because the intake of food is already a painful and difficult activity because of the acute mucositis. The return of taste acuity is very slow, only beginning several months after therapy ceases. Full recovery may take more than 1 year.

Muscle damage and eventual replacement with fibrous tissue occasionally develops (Figure 11-33). This, combined with fibrosis within the temporomandibular joint, can result in a reduced oral opening and trismus. Both conditions are difficult to correct and are best controlled by careful planning of the fields and fractionation of the dose of radiation and physiotherapy to the muscles during the recovery phase.

Of greater concern are the complications of post-treatment necrosis and gangrene of the soft tissue. Because blood vessels are particularly sensitive to ionizing radiation, endarteritis and periarteritis are common occurrences during treatment. These conditions result in permanently damaged vessels that have either significantly reduced blood flow or become completely blocked. Additionally, the capacity for new vessel formation in the affected tissue is reduced. On occasion, the mucosa becomes atrophic, with the



FIGURE 11-32
Osteoradionecrosis. Fragment of necrotic bone (sequestrum) exteriorized in an area of advanced periodontal disease in a patient who received radiotherapy to the region.

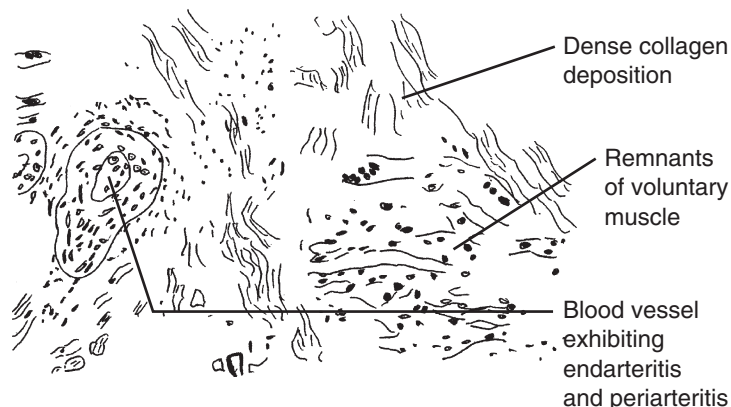
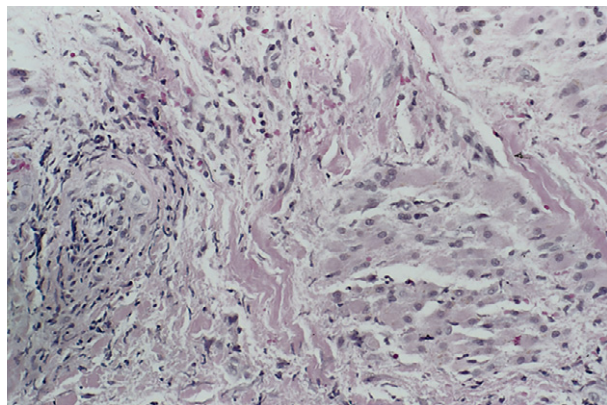


FIGURE 11-33
Soft tissue radiation injury. Photomicrograph of submucosal tissue within an irradiated field containing a blood vessel exhibiting severe endarteritis and periarteritis (*right*) and myositis with replacement of damaged tissues with scar tissue (*fibrosis*).

frequent development of ulcers that are slow to heal or may undergo ischemic necrosis followed by large areas of sloughing. The wearing of dentures or other appliances should be delayed for at least 1 year. Surgical procedures in areas previously irradiated should be avoided or conservatively undertaken because of the reduced vascularity and ability to heal.

CHEMICAL INJURIES

TEETH

Tetracycline

The ingestion of tetracycline during the mineralization of the organic matrix of developing deciduous and permanent teeth, bone, or cartilage results in permanent incorporation of the antibiotic into the mineral component of these tissues. Although this is not a serious problem in bone or cartilage because they are not visi-

ble, the teeth usually become cosmetically disturbing to the patient. The affected teeth exhibit yellowish to brownish-gray diffuse bands of discoloration that are located within the tooth structure and not on the surface. The intensity and distribution of color vary, depending on the specific form of tetracycline taken and the duration of the administration.

Chlortetracycline tends to cause a brownish-gray color (Figure 11-34, A), whereas oxytetracycline and tetracycline give a yellowish color (Figure 11-34, B), which is the least noticeable. In young teeth the color is most intense and unattractive but tends to fade slightly with time to a light brown. With the loss of intensity of the coloration, the ability to diagnose tetracycline staining when using ultraviolet (UV) light to demonstrate its fluorescent property also diminishes.

To prevent discoloration of the teeth, alternative types of antibiotics for treatment of infections is recommended for women who are in the second and third trimesters of pregnancy and for children under the age of 7 years. External bleaching is of little value, because the tetracycline is complexed with the calcium ions that are deposited during the mineralization of the enamel and dentin and thus is not accessible like surface stains. The ability of tetracyclines to become incorporated into bones and teeth within hours of ingestion has been a useful experimental tool for labeling microscopic events according to time. When teeth are sectioned and examined microscopically with UV light, narrow bands or rings are seen coinciding with the part of the tooth developing at the time of administration (Figure 11-35).



FIGURE 11-34
Tetracycline discoloration. Gray-brown (A) and yellowish-gray (B) discolorations of the cervical third of the maxillary anterior teeth in patients with chronic conditions requiring prolonged treatment with tetracycline during early childhood.

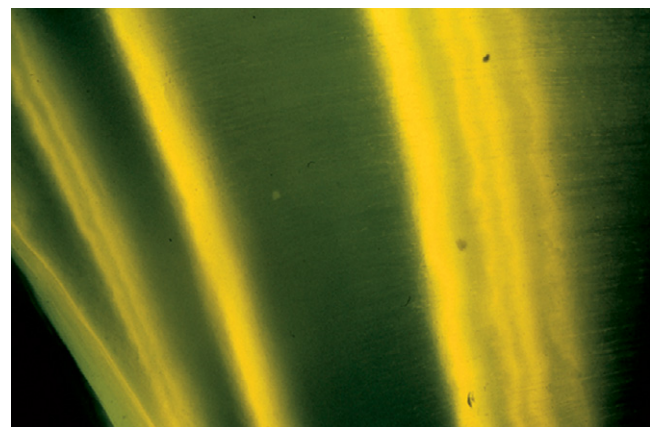


FIGURE 11-35
Tetracycline discoloration. Section of a nondecalcified tooth of a patient periodically treated with tetracycline during childhood viewed with ultraviolet light microscopy exhibiting dentin containing yellowish fluorescent bands of tetracycline deposited during tooth development.

Congenital Porphyria

Although multiple types of porphyrias exist, only the congenital type produces the distinct discoloration of the teeth. Discoloration occurs because excess porphyrins are present in the blood during the mineralization of the teeth. Congenital porphyria is inherited as an autosomal recessive trait that is responsible for the development of a defective pathway for the metabolism of hematoporphyrins, resulting in the accumulation of excessive porphyrins in the blood and urine. The porphyrins become deposited in the skin and the developing teeth and bones. Affected teeth are pinkish brown; when viewed with UV light fluoresce they are bright scarlet. Sectioned teeth exhibit similar findings with normal and UV light and show the fluorescence in bands conforming to the incremental growth lines. The skin is also severely affected, becoming light brown and extremely sensitive to sunlight. The photosensitivity is expressed as large bullous lesions that often heal with scarring. It is not uncommon for patients with porphyria to have extensively scarred limbs and faces by the time they reach adulthood.

Biliary Atresia

Biliary atresia is an uncommon congenital condition that consists of a narrowing of the ductal elements of the biliary system of the liver, resulting in elevated bilirubin levels in the blood. Complete or nearly complete congenital blockage is fatal, and those most severely affected die within months of birth. Patients with lesser degrees of atresia appear jaundiced and will exhibit discolored teeth, particularly in the primary dentition. In these patients the teeth will have a dark greenish color with the roots more intensely stained than the crowns. The degree and distribution of tooth discoloration depends on the ability to manage the medical condition during tooth development in both the deciduous and permanent dentition.

Erythroblastosis Fetalis

Erythroblastosis fetalis is a hemolytic anemia that begins in utero. It results from incompatible factors in the blood of the mother and the fetus. An Rh-negative mother will develop antibodies against the erythrocytes of an Rh-positive fetus. The antibodies transgress the placental barrier, attacking and destroying the fetal erythrocytes. The result of the extensive hemolysis is the greatly elevated levels of the biliverdin and bilirubin blood pigments. These pigments become deposited in both the skin and the developing teeth of the fetus. Not all Rh incompatibilities result in tooth changes, because the blood levels of pigment must be very high

and present in the fetus between 4 and 7 months intrauterine. Only primary teeth are affected, with colors varying from green and bluish green to yellowish gray. The dentin is primarily affected. When dentin is severely involved, some enamel hypoplasia may also be present. The color fades in time but is still noticeable. With immediate blood transfusion at birth, discoloration is minimal. The permanent teeth are usually not affected.

GINGIVA

Chemical effects on gingiva may be in two forms: (1) pigmentations that result from the ingestion of medications containing heavy metals such as bismuth, silver, mercury, gold, copper, and zinc or (2) hyperplasia of the collagenous component. Except for bismuth, the pigmentation effects of chemicals are rarely seen today, because these compounds have been replaced as antimicrobials by antibiotics. Bismuth is still widely used as an antidiarrheal agent, but unless it is taken in excess, the only resulting pigmentation is in the form of a transitory brown staining of the dorsal tongue. If for some reason the patient has experienced extensive intake of heavy metals, such as during occupational exposure, it is usually present in the marginal gingiva, where it appears as a thin, dark-brown or gray line.

In recent years the medications that most commonly affect the gingiva are those that have the overproduction of collagen as a side effect. They are capable of inducing such extensive gingival hyperplasia that if left untreated would rapidly lead to advanced periodontitis with eventual premature loss of the dentition. These medications consist of phenytoin, cyclosporine, and calcium channel-blocking medications such as nifedipine, each administered for different purposes in the management of systemic conditions.

Phenytoin

Phenytoin (Dilantin) is used to depress selected brain pathways without affecting the body's sensory functions. It is effective as an anticonvulsant and thus is widely used in patients with epilepsy, brain tumors, and other central nervous system (CNS) conditions that are prone to produce seizures.

The mechanism of the oral side effect of gingival enlargement is not completely known. Some research shows a direct effect by phenytoin on the fibroblasts responsible for collagen production. Other research indicates that phenytoin acts to destabilize the cell wall of the gingival mast cells, inducing excessive degranulation and release of histamine, heparin, and other ingredients that stimulate the fibroblasts to produce excessive collagen.

The incidence of gingival hyperplasia is in the range of 40% to 50%. In those patients subject to the side

effect, the hyperplastic condition becomes obvious 2 to 3 months after the administration of phenytoin, with the enlargement reaching its maximal severity in 12 to 18 months. There does not seem to be a close relationship between the dose of phenytoin and the severity of the enlargement. It has been generally thought that patients lacking adequate oral hygiene will develop a more rapid and severe form of the condition. Some patients develop extensive enlargements in the absence of gingivitis, developing lesions in edentulous areas. Hereditary factors are considered responsible for the degree to which some patients are affected and whether they become affected at all.

Enlargement begins in the interdental papillae as a bulbous or lobular growth, extending both buccally and lingually. The anterior part of the mouth usually becomes more involved than the posterior. The growths can enlarge to cover part or all of the crowns of the teeth, interfering with mastication. When not inflamed, the enlarged gingiva appears pink in color with a normally stippled surface. The enlargement is firm with little resiliency and does not bleed when probed. In contrast, inflamed gingiva not caused by phenytoin enlargement is dark red, edematous, friable, and bleeds easily. Treatment consists of surgical removal of excessive tissue as necessary to allow function and maintenance of oral hygiene.

Cyclosporine

Cyclosporine, a compound derived from soil fungi, has a selective immunosuppressive effect on the T lymphocyte helper cells but without bone marrow suppression. It is primarily used to reduce the chance of rejection in organ transplant patients and occasionally used in the treatment of some autoimmune diseases. Because it has nephrotoxic and hepatotoxic effects, blood levels of patients who are taking the medication are carefully monitored.

Within the oral cavity, cyclosporine has the frequent side effect of inducing generalized gingival hyperplasia (Figure 11-36) and perioral hyperesthesia. In some clinical studies, generalized gingival enlargement was found in 50% of all patients, with incidences approaching 100% of patients under 20 years of age. Some gingival enlargement is apparent within 1 to 3 months of the initiation of cyclosporine therapy, becoming maximized at about 1 year.

The mechanism of cyclosporine-induced gingival hyperplasia is not well understood. Because not all patients exhibit gingival enlargement, selective stimulation of fibroblasts is suspected. In some cases an increase in the noncollagenous extracellular matrix has been found. This latter finding is consistent with the clinical observation that with cessation of the medication, gingival enlargement often subsides substantially.



FIGURE 11-36

Cyclosporine-induced gingival hyperplasia. Renal transplant patient with generalized nodular gingival overgrowth.

The clinical appearance of cyclosporine-induced gingival hyperplasia is similar to that induced by phenytoin. It is more pronounced in the anterior aspect of the mouth and can enlarge to cover the crowns of the teeth. The extent of inflammation depends on the degree of local irritants. Because cyclosporine is an immunosuppressant, it is thought by some sources that the incidence of progressive periodontitis is enhanced because of the compromised defense system within the gingiva. At present, no experimental evidence supports this.

The ideal treatment for cyclosporine-induced gingival hyperplasia is withdrawal of the medication; however, this is seldom possible. The enlargements can be minimized with meticulous oral hygiene. Periodically, enlargements that interfere with mastication will require surgical excision.

Nifedipine

Nifedipine is a commonly used calcium channel-blocking agent in the treatment of cardiovascular disorders such as angina pectoris and hypertension. It acts by inhibiting calcium ion influx in the smooth muscle of cardiac tissue and blood vessel walls without changing the serum calcium concentration. Therefore it is useful to selectively reduce contraction of some smooth muscles and is effective as a vasodilator. It enables the relaxation of blood vessels, thereby reducing vascular hypertension and the tendency for spasms in coronary arteries. This allows for better blood flow, thereby increasing oxygen levels to cardiac muscle. Because it acts on all smooth muscle, it has the generalized side effects of hypotension, weakness, dizziness, and syncope in some patients. The notable side effect within the oral cavity is a tendency for gingival enlargement.



FIGURE 11-37
Nifedipine-induced gingival hyperplasia. Interdigital gingiva exhibits nodular fibrous hyperplasia in the region of the mandible containing teeth.

The manner in which nifedipine and the other calcium channel blockers induce excessive gingival hyperplasia is thought to be through altered calcium influx into fibroblasts interfering with the production of collagenase. Thus collagen is not degraded and accumulates.

Between 25% and 50% of patients taking the medication will develop gingival enlargement. The enlargement begins 1 to 3 months after treatment starts and does not appear to be correlated with the dose. The gingival hyperplasia of nifedipine is clinically similar to that of phenytoin and cyclosporine. It is nodular and firm, originating in the interdental papillae of the anterior teeth (Figure 11-37). The enlargements are more severe when local irritants such as plaque, calculus, and defective fillings and crowns are present.

The best treatment for calcium channel blocker-induced gingival hyperplasia is the substitution of another vasodilator. If this is not possible, gingivectomy and meticulous oral hygiene can be used to control the severity of the condition.

MUCOSAL TISSUE

Amalgam

The accidental implantation of silver-containing compounds into the mucosal connective tissue usually results in a permanent grayish-black pigmentation, commonly referred to as *amalgam tattoo*. These pigmentations are notable, because they are similar in appearance to melanin-containing pigmentations, which are of concern to the clinician and patient. The most common



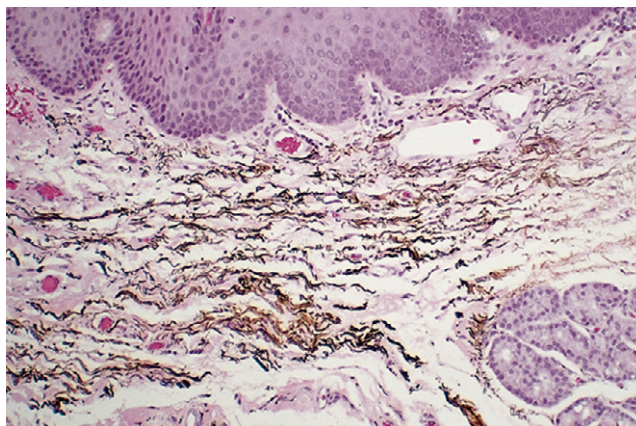
FIGURE 11-38
Amalgam tattoo. Focal gray-black pigmentation resembles a melanin-producing lesion on the buccal gingiva in the area of a previous extraction and large restoration.

source of embedded silver compounds is amalgam, hence the name amalgam tattoo. Amalgam is presently the most commonly used material for dental restorations and is composed of a mixture of silver, mercury, and tin. It enters the tissue accidentally, either through a laceration in the mucosa during a dental procedure, by falling into a socket during the extraction of a tooth, or by inadvertent compaction into the gingival sulcus while a restoration is placed (Figure 11-38). Amalgam is also used to seal the apex of a nonvital tooth after apicoectomy. Because this requires an intraosseous surgical procedure during which amalgam is intentionally placed within the bone and adjacent soft tissue, the pigmentation is often apparent on the surface (Figure 11-39). Larger fragments of amalgam may sometimes be discernible on radiographs. Absence of radiographic evidence of amalgam does not rule out the possibility of an amalgam tattoo, because the particles are often too fine or widely dispersed to be visible. Clinical pigmented lesions that are not visible on radiographs should be biopsied to ensure that they do not represent an early melanoma.

The microscopic features of amalgam tattoos vary depending on the size of the particles and the quantity present. When larger fragments are present, a granuloma consisting of multinucleated giant cells, lymphocytes, and increased fibrosis surrounds the foreign material. When only smaller dustlike particles are present, they are usually engulfed by individual macrophages without the formation of distinctive granulomas. The fine particles are also found within the cytoplasm of a large number of cells and tissues, including muscle,

**FIGURE 11-39**

Amalgam tattoo. Diffuse area of blue-gray pigmentation of submucosal tissue over the apex of a nonvital central incisor previously treated by apicoectomy and an amalgam retrofill of the tooth apex.

**FIGURE 11-40**

Amalgam tattoo. Microscopic appearance of submucosal tissue exhibiting linear staining of elastic and reticular fibers with a dark-brown silver precipitate.

nerve, blood vessel walls, and collagen. Some tissues, particularly elastic fibers and the basement membrane, chemically interact with amalgam incorporating the liberated silver as a fine linear deposit of brown precipitate (Figure 11-40).

Once the diagnosis has been made, additional treatment is necessary only if the pigmentation is cosmetically unacceptable. In some instances if the amalgam particles are large, they should be removed to prevent a further foreign-body response or a source of irritation, especially if a prosthetic appliance is to be placed over the area.

Graphite

Graphite pigmentations are similar to amalgam pigmentations in size and color but tend to occur in different locations. They are caused by accidental tissue punctures of the mucosa with a pencil. At the time of puncture, fine particles of carbon are permanently deposited in the submucosal tissue.

Most pigmentations of this origin are located in the anterior part of the mouth and on the soft palate, where they may be associated with a perforation. The pigmentations are small, usually of several millimeters in diameter, grayish black, and circular. The microscopic appearance differs from that of an amalgam tattoo, because no large fragments are present to induce a foreign-body response. Inflammation, granuloma formation, and multinucleated giant cells often associated with amalgam are absent. Because graphite is an inert material, no chemical interaction with the elastic fibers or basement membrane occurs, as it does with the silver contained within amalgam. The fine carbon particles are nearly all

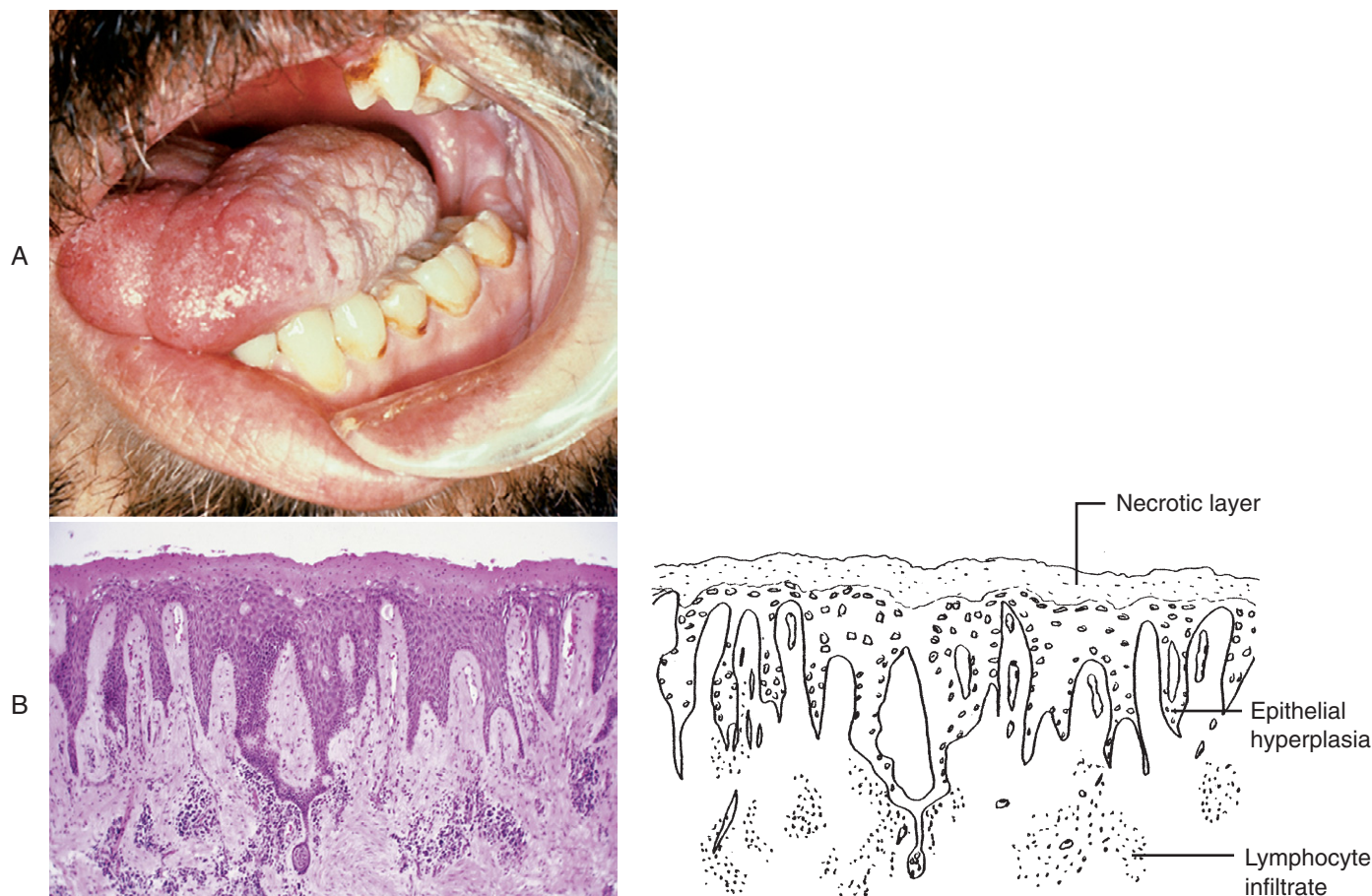
found within the cytoplasm of macrophages and other tissue cells capable of phagocytosis. After biopsy no treatment is necessary unless the patient wishes the area removed for cosmetic reasons.

CHEMICAL BURNS

Acetylsalicylic Acid

The beneficial effect of placing acetylsalicylic acid (ASA) on the alveolar processes directly over the roots of a tooth that is the source of severe pain is a commonly held misconception. It is based on the belief that the analgesic is able to penetrate the mucosa and cortical plate of bone and act directly on the nerve bundle of the offending tooth. Sometimes the ASA is placed within the cavitation of a carious tooth. In either location the tablet is slowly dissolved, liberating a concentrated acidic solution in the immediate area that becomes diluted and buffered in the saliva farther away from the painful area. Most of the relief that patients receive is believed to be because the solution is swallowed and absorbed systemically.

Because in many cases the ASA is in direct contact with the tongue and buccal mucosa, the soft tissue will appear white and friable, superimposed against an erythematous background with associated symptoms of burning (aspirin burn) (Figure 11-41, A). If the lesion is severe, removal of the superficial white layer may reveal a bleeding erosive base. The concentrated solution produces necrosis of the surface layers of the epithelium and an inflammatory response of the deeper connective tissue (Figure 11-41, B). Upon cessation of the practice, healing occurs in 1 to 2 weeks.

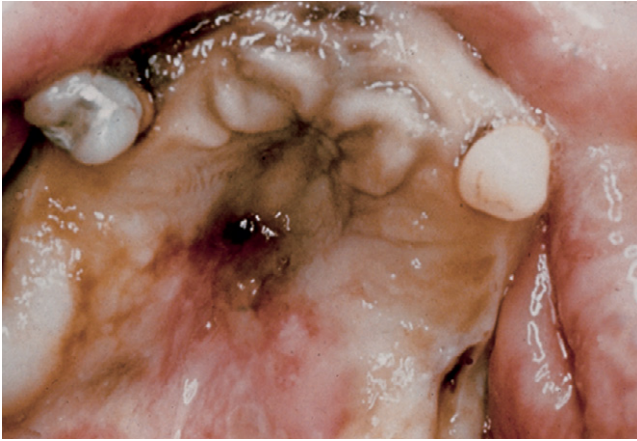
**FIGURE 11-41**

Aspirin burn. **A**, The lateral surface of the tongue and buccal mucosa with a white, wrinkled surface and an erythematous background resulting from prolonged contact with acetylsalicylic acid placed adjacent to a painful tooth. **B**, Microscopic appearance of chemically injured tissue demonstrating a superficial layer of necrotic epithelial cells and connective tissue diffusely infiltrated with plasma cells and lymphocytes.

Other Medications

Many other medications used in dentistry can also produce chemical burns of the perioral facial skin and mucosal tissue if inadvertently dropped on these surfaces during use. Some medications such as phenol (carbolic acid), which is used as a disinfectant, or silver nitrate, which is often deployed as a cauterizing agent, are capable of superficial necrosis when dropped on the tissue in concentrated form. Other chemical agents are used as astringents (trichloroacetic acid) for gingival retraction and when overused result in tissue necrosis of the mar-

ginal gingiva. Some patients have misused denture-cleansing agents that contain concentrated detergent and oxidizing agents by placing the appliances in their mouths without properly rinsing off the excess cleaner (Figure 11-42). In some patients, overuse of some types of mouthwash and toothpaste can cause a superficial necrosis of the superficial mucosa (slough) (Figure 11-43). This can be easily wiped off temporarily by passing the finger over the mucosa. In all of these situations the severity of the condition depends on the concentration of the medication, the duration of the application, and the biologic differences in individuals.

**FIGURE 11-42**

Severe chemical burn. Large area of superficial necrotic soft tissue developed after patient placed a partial denture in the mouth without removing denture-cleansing agent.

**FIGURE 11-43**

Mild chemical burn. Superficial thin, white membrane of necrotic epithelial cells on the buccal mucosa as the result of overuse of mouthwash. The mucosal slough can be easily removed by wiping with a finger or gauze.

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12 *Diseases of Blood*

CHAPTER OUTLINE

RED BLOOD CELLS

Anemia
 Iron Deficiency Anemia
 Pernicious Anemia
 Sickle Cell Anemia
 Thalassemia
 Fetal Erythroblastosis

WHITE BLOOD CELLS

Leukopenia
 Agranulocytosis
 Cyclic Neutropenia
 Neutrophil Function Disorders
 Chronic Granulomatous Disease of Childhood
 Leukocytosis
 Bacteria-Associated Leukocytosis
 Virus-Associated Leukocytosis
 Infectious Mononucleosis
 Neoplasms
 Leukemia
 Hodgkin Lymphoma
 Non-Hodgkin Lymphoma
 MALT Lymphoma
 Burkitt Lymphoma
 Multiple Myeloma

BLEEDING DISORDERS

Platelet Disorders
 Thrombocytopenia
 Thrombasthenia
 Capillary Fragility
 Vitamin C Deficiency (Scurvy)
 Hereditary Hemorrhagic Telangiectasia
 Coagulation Disorders
 Hemophilia

ADDITIONAL KEY TERMS

Achlorhydria
 Acquired coagulopathy
 Afibrinogenemia
 Angiocentric lymphoma
 Atypical lymphoproliferative disease
 Band cell
 Graft-versus-host disease
 Granulocytic sarcoma
 Hunter glossitis
 Mononuclear leukocytosis
 Mycosis fungoides
 Myelodysplastic syndrome
 Neutrophilic leukocytosis
 Pautrier microabscess
 Philadelphia chromosome
 Plummer-Vinson syndrome
 Polycythemia
 Rendu-Osler-Weber syndrome
 Sézary syndrome



RED BLOOD CELLS

The average male has approximately 6 million red blood cells/mm³ of whole blood, whereas the average female has somewhat less, about 5 million cells/mm³. Erythrocytes, by virtue of their hemoglobin content, transport oxygen to the tissue and are involved in the transport of carbon dioxide (CO₂) away from the tissue to be exhaled through the lungs. Deficiencies in the capacity to transport oxygen are referred to as *anemias* and may be caused by a reduction in the number of red cells, decreased size of the individual cells, or reduced levels of hemoglobin. Most of the disorders affecting red blood cells are anemias.

A neoplastic process of hematopoiesis in which erythrocytes are synthesized by the bone marrow in increased numbers is called *polycythemia*. Most of these red blood cell disorders cause generalized systemic changes; however, many may be associated with oral or osseous lesions, the latter of which may be observed on dental radiographs.

ANEMIA

Anemia occurs when the oxygen-carrying capacity of the erythrocyte is hampered. This can occur as a consequence of a decreased number of red cells, a decrease in their size, or a decrease in their hemoglobin content. The specific alterations may be induced by a variety of disease factors, which can be divided into three main areas: (1) excessive blood loss as the result of trauma, internal hemorrhaging, or spontaneous hemolysis (which can be a consequence of autoimmune mechanisms in which antibodies attach to erythrocytes, fix complement, and lyse them); (2) genetic diseases in which the hemoglobin is defective, leading to a pathologic cell shape that predisposes them to lysis; and (3) nutritional deficiencies in which precursor substances necessary for hemoglobin synthesis are lacking in the diet or fail to be absorbed in the intestines.

In the laboratory, anemia is assessed three ways: (1) by performing a red blood cell count, (2) by measuring the total packed cell volume (the hematocrit), and (3) by quantifying the amount of hemoglobin (Figure 12-1). These three parameters are formulated to yield the red cell indices. These indices represent calculations that aid in determining the size and hemoglobin content of an individual's red blood cell. Although the total red count may be within normal limits, the patient may still suffer from decreased oxygen transport capacity if the individual cells are too small. In this case the hematocrit would be decreased. Even though present in adequate numbers, because the test is measuring the total volume of smaller cells, it would show a lower volume or mass within the total blood sample. Anemia characterized by small cells is termed *microcytic anemia*.

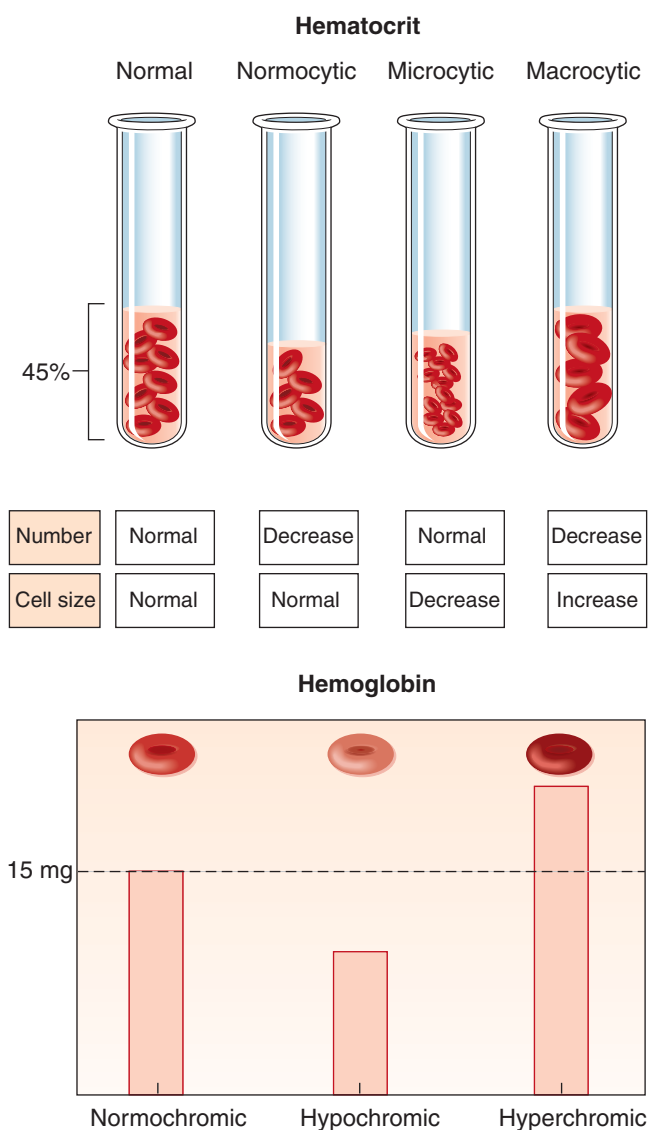


FIGURE 12-1

Anemia. *Top:* The hematocrit represents the packed cell volume of red cells and is expressed as a percentage of whole blood. The hematocrit is decreased when the red cell count is decreased or when erythrocytes are small. *Bottom:* The hemoglobin is a measure of the oxygen-carrying capacity of the erythrocyte and in any given cell may be (left to right) normal (normochromic), decreased (hypochromic), or elevated (hyperchromic).

Alternatively, if the individual cells are of normal size but contain insufficient amounts of hemoglobin, the patient will still be anemic. Anemia caused by decreased hemoglobin content within normal-sized cells is referred to as *hypochromic anemia*. When the total number of red blood cells is decreased and the bone marrow attempts to compensate by synthesizing larger cells with an increased concentration of hemoglobin, the anemia is said to be a *macrocytic and hyperchromic anemia*.

Genetic abnormalities of hemoglobin are assessed by more sophisticated laboratory procedures such as hemoglobin electrophoresis. When subjected to an electric current (electrophoresis), abnormal hemoglobins migrate at different rates and can be detected in this manner. The definitive diagnosis for a specific type of anemia is therefore based on an assessment of a variety of clinical and laboratory tests.

Iron Deficiency Anemia

IRON DEFICIENCY ANEMIA: A lack of red blood cells and hemoglobin because of inadequate dietary intake of iron.

The most common form of anemia is secondary to iron deficiency. This is most frequently encountered in women, particularly when the menstrual cycle is heavy and hematopoiesis takes place in the absence of adequate dietary iron intake. The erythrocytes of patients with the iron deficiency will be both hypochromic and microcytic. In addition, the total number of erythrocytes may be decreased. Therefore the red cell count, hematocrit, and hemoglobin will be at levels below normal.

CLINICAL FEATURES

Patients suffering from iron deficiency anemia will manifest symptoms of tiredness, weakness, and malaise. Increased respiratory rate may also be a finding. The primary physical change will be tissue pallor, which may be more obvious on the mucous membranes than on the skin. Oral manifestations of iron deficiency anemia include bald tongue, atrophic mucositis, angular cheilitis (probably secondary to candidiasis), and aphthous ulcerations; signs are similar to those found more prominently in patients with pernicious anemia. Some patients with iron deficiency anemia, particularly those of Scandinavian descent, experience atrophic mucositis of the upper aerodigestive tract, including the oropharynx; these patients are predisposed to oropharyngeal squamous cell carcinoma. The coexistence of iron deficiency anemia, mucosal atrophy, and carcinoma is quite rare and is referred to as the *Plummer-Vinson syndrome*.

LABORATORY FINDINGS

The blood exhibits a decrease in total red cell count, hematocrit, and hemoglobin. A stained microscopic slide of a blood smear may show evidence of microcytic erythrocytes. Iron levels are decreased in the blood. Serum iron binding capacity and transferrin saturation should be assessed, particularly when overt hypochromic microcytic anemia is not obvious. Serum iron decreases as the iron binding capacity increases with a concomitant drop in transferrin saturation. The dorsal surface of the tongue may exhibit histopathologic features of atrophy, with loss of the usual tongue papillae. The spinous layer and sub-

mucosa in atrophic tongues show a mixed leukocytic infiltrate in the connective tissue.

TREATMENT

Once the diagnosis has been made, dietary iron supplementation is the usual treatment. Iron supplementation will generally reverse the anemia within a few weeks of therapy. Development of carcinoma in the Plummer-Vinson syndrome requires surgical and radiotherapeutic interventions.

Pernicious Anemia

PERNICIOUS ANEMIA: Impaired red blood cell maturation secondary to insufficient vitamin B₁₂ as the result of a defective intrinsic factor required for its absorption through the intestinal wall.

Erythrocyte maturation within the bone marrow depends on the availability of adequate amounts of folic acid and vitamin B₁₂. These cofactors are essential for the maturation of the erythrocyte. Although folic acid deficiency may be ameliorated by nutritional therapy, vitamin B₁₂ deficiency is rarely the consequence of inadequate intake of the vitamin. Instead, in pernicious anemia, the patient is affected by a defective absorption factor referred to as the *intrinsic factor*. This intestinal transport protein is required for absorption of vitamin B₁₂. The gastric mucosa is atrophic and fails to secrete appropriate amounts of hydrochloric acid, a condition referred to as *achlorhydria*. Both folate deficiency and B₁₂ malabsorption are causes of megaloblastic anemia.

CLINICAL FEATURES

Pernicious anemia can be a severe disease, causing extreme malaise and tiredness. The patient will exhibit pallor and may also suffer sensory neurologic disorders manifested as paresthesia. Motor function may also be impaired. The neurologic symptoms are also related to the lack of vitamin B₁₂. A characteristic finding in pernicious anemia within the oral cavity, occurring in 50% of cases, is depapillation of the tongue, a condition known as *Hunter glossitis*. The filiform papillae undergo atrophy, and the tongue appears bald and smooth with an erythematous cast (Figure 12-2). The oral mucosa in general may be atrophic and exhibit pallor. Angular cheilitis is also seen and is usually associated with a chronic atrophic form of candidiasis. Other oral changes that are encountered in megaloblastic anemias are oral aphthouslike ulcerations, focal red macules, and mucosal pigmentations.

LABORATORY FINDINGS

The total red count is significantly decreased with a disproportionate change in the hematocrit and hemoglobin content. To compensate for the decrease in vitamin

**FIGURE 12-2**

Pernicious anemia. Atrophy of the filiform papillae of the dorsal surface of the tongue (bald tongue).

B₁₂, the individual erythrocytes that are synthesized are large and incorporate greater than normal amounts of hemoglobin. Therefore pernicious anemia is classically a hyperchromic macrocytic anemia, a feature shared with folic acid deficiency. On blood smears the cells will be larger than normal and will stain darker, owing to their increased hemoglobin content. Bone marrow aspirates disclose the presence of megaloblasts, which are large erythrocyte precursor cells typical of folate and vitamin B₁₂ deficiency anemias. Gastric analysis will reveal achlorhydria. Because folate and vitamin B₁₂ deficiencies are characterized by macrocytic hyperchromic anemia, serum folate and B₁₂ levels must be obtained to distinguish between the two types of anemia.

Microscopically the tongue exhibits a loss of fungiform and filiform papillae, epithelial atrophy, and submucosal inflammation.

TREATMENT

Pernicious anemia patients lack the intrinsic factor necessary for absorption, and therefore increased dietary supplementation will not reverse the signs and symptoms. For this reason intramuscular injections of vitamin B₁₂ must be initiated. Monthly injections are usually adequate to allow for normal hematopoiesis.

Sickle Cell Anemia

SICKLE CELL ANEMIA: *An inherited defect in the structure of the hemoglobin molecule causing the erythrocyte to assume a crescent shape ("sickle") and to undergo lysis.*

Inherited as an autosomal recessive disease, sickle cell anemia is characterized by a point mutation in the hemoglobin gene, creating an abnormal hemoglobin molecule (Hb S). The point mutation causes a substitution of the

**FIGURE 12-3**

Sickle cell anemia. Radiographic appearance exhibiting abnormal trabecular pattern.

amino acid valine for glutamine in the gene. The resultant hemoglobin is defective; the usual discoid shape is lost, leading the cells to assume a crescent or sickle shape. These cells are prone to agglutinate and clog the small-caliber vascular channels. When such an event occurs, usually in the context of low oxygen pressure, a sickle cell crisis may evolve and can be fatal. More commonly, the sickle cells tend to hemolyze, causing jaundice.

Sickle cell anemia is encountered primarily among blacks; when it occurs as a heterozygous genotype (Hb A, Hb S), the affected individual shows only minor signs of the disease and is said to harbor the *sickle cell trait*. Individuals who inherit both recessive genes in the homozygous genotype manifest the full-blown hemolytic disease, sickle cell anemia (Hb S, Hb S). Other rare forms of sickling disease have been identified.

CLINICAL FEATURES

Patients affected with the trait only rarely show any significant signs or symptoms, but they may have a slightly lowered red blood cell count. Those with the homozygous form of sickle cell anemia share signs and symptoms in common with other anemias, including malaise and weakness. The sclera may be yellowed, owing to the accumulation of unconjugated bilirubin within the blood as a consequence of hemolysis. As more cells hemolyze and the oxygen tension in the blood decreases, the tendency for sickling is greater. Muscle rigidity and unconsciousness characterize a sickle cell crisis. Widespread ischemia may develop, leading to death.

No specific oral mucosa problems are found in sickle cell anemia; however, bone changes are frequently identified on dental and skull radiographs. A compensatory increase in hematopoiesis may occur, leading to osseous changes. In the skull, numerous small icicle-like spicules may be identified across the

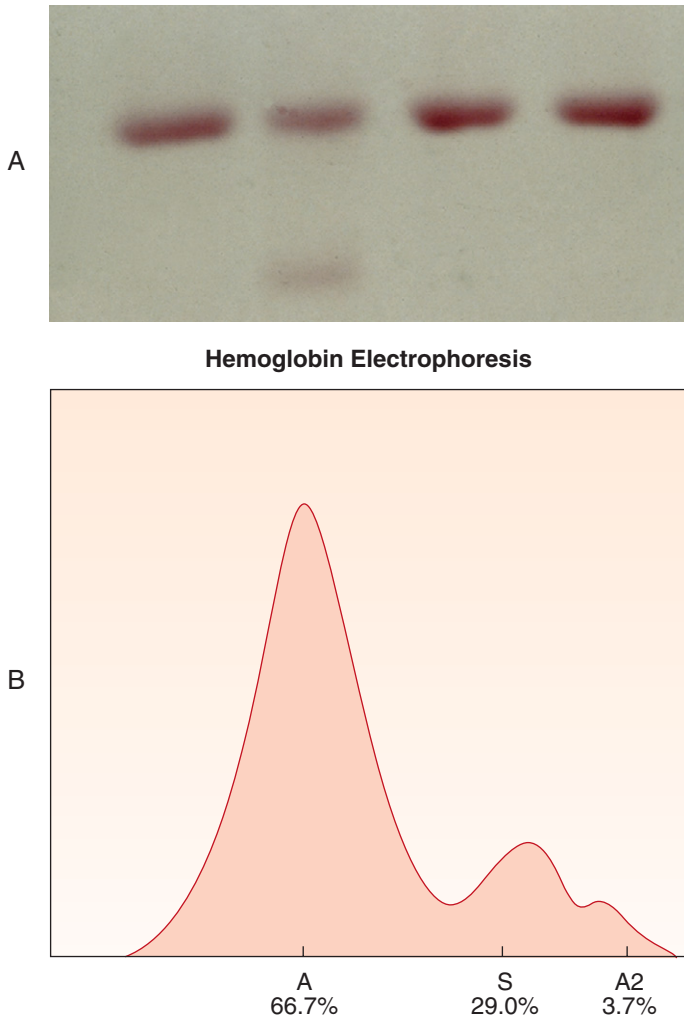


FIGURE 12-4

Sickle cell anemia. **A**, Hemoglobin electrophoresis. Lanes 1, 3, and 4 (left to right) have one band of normal hemoglobin A (Hb A); lane 2 shows two bands—one for Hb A and a second for hemoglobin S, indicating the presence of a heterozygous sickle cell trait. **B**, Graph of findings of **A** showing two major peaks for Hb A and hemoglobin S, respectively.

calvarium, yielding a so-called “hair-on-end” effect. On dental radiographs, although not pathognomonic, stepladder trabeculae are often seen between contiguous posterior teeth (Figure 12-3).

LABORATORY FINDINGS

The total red blood cell count, hemoglobin, and hematocrit are decreased; on differential smears, sickle cells may be identified. Characteristic concomitant findings include elevated unconjugated bilirubin and urine urobilinogen. Hemoglobin electrophoresis will disclose the presence of normal hemoglobin and hemoglobin S in those with the sickle cell trait, whereas the individuals with homozygous sickle cell disease will show a single hemoglobin S band on electrophoresis (Figure 12-4).

TREATMENT

Transfusions and bone marrow or stem cell transplantation are current methods of treatment. Gene therapy may prove to be an important intervention in the future. At present, individuals with the disease must be closely monitored for the development of sickle cell crisis. In these instances hospitalization is required, with administration of oxygen and blood transfusions.

Thalassemia

THALASSEMIA: An inherited defect in either the α or β chain of the hemoglobin molecule resulting in hemolysis.

Also referred to as *Mediterranean* or *Cooley anemia*, thalassemia is a heritable disease in which the gene for the hemoglobin molecule is mutated with generation of defective forms of the α or β chain of hemoglobin A (Hb A). Individuals of Mediterranean region descent are the most prone to develop this form of anemia. Like sickle cell anemia, thalassemia is an autosomal recessive disease; therefore heterozygous individuals only carry the trait and are said to suffer from *thalassemia minor*. *Thalassemia major* occurs in the homozygous genotype when both genes are affected. Thalassemia major is lethal, whereas those with the minor form show only mild ill effects.

CLINICAL FEATURES

Heterozygous individuals with thalassemia minor show lesser signs and symptoms of anemia. Those with homozygous disease are lethargic, manifesting weakness and malaise. Because the defective cells are prone to hemolysis, the patients may show evidence of jaundice; death often occurs in adolescence. Other than a tendency toward pallor, other soft tissue changes are not observed. Osseous changes are radiographically demonstrable in the jaws and on skull films. These changes are only seen in thalassemia major. The calvarium shows altered trabeculation with osteophyte formation, yielding a “hair-on-end” effect. On dental films the trabeculation may be markedly altered with an unusual “honeycomb” radiolucent appearance (Figure 12-5).

Bones containing this multilocular configuration show no evidence of enlargement or expansion, unlike various tumors that cause similar radiologic changes. In some cases, enlargement of the zygomatic bones can be seen, yielding a mongoloid facies.

LABORATORY FINDINGS

The hemoglobin, hematocrit, and red blood cell count will be decreased, and the unconjugated bilirubin will be elevated. Hemoglobin electrophoresis will disclose the characteristic pattern for the various forms of thalassemia major.

**FIGURE 12-5**

Thalassemia. Radiograph of characteristic “honeycomb” radiolucencies bilaterally in the mandible and in the left maxilla.

TREATMENT

Regular transfusion and chelation therapy are the primary modes of treatment. Gene therapy and bone marrow transplantation may hold promise for the future.

Fetal Erythroblastosis

FETAL ERYTHROBLASTOSIS: *A form of hemolytic anemia that occurs in utero when maternal antibodies develop against antigens on fetal red blood cells and then cross the placenta, inducing hemolysis.*

Another form of hemolytic anemia is fetal erythroblastosis. As opposed to sickle cell and thalassemia anemias, erythroblastosis is not caused by a genetic defect; instead it represents an immunologic response with antibody- and complement-mediated hemolysis. Although the disease is often referred to as *Rh-factor disease*, the ABO blood group antigens may also initiate the adverse reaction. In the classic form of the disease the pregnant mother lacks the Rh factor, whereas the fetus inherits the Rh factor from his or her father. A minor tear in the placenta will allow fetal blood to be introduced into the maternal circulation, and the mother then makes antibodies to the Rh-positive erythrocytes. The first birth is usually of no consequence; however, when a second pregnancy occurs in a mother who now has circulating anti-Rh antibodies, mingling of blood may result in the passage of anti-Rh factor antibodies into the fetal circulation. These antibodies will attach to the fetal erythrocytes, fix complement, and cause hemolysis. As mentioned previously, a similar phenomenon may occur with ABO incompatibility between the fetus and mother. As erythrocytes continue to hemolyze, the bilirubin levels increase and kernicterus may develop, leading to neural damage and retardation. For this reason affected newborns are transfused immediately.

CLINICAL FEATURES

Fetal erythroblastosis is diagnosed on delivery of the newborn. The affected infant will be cyanotic and jaundiced. Cyanosis is usually readily seen on the skin and mucous membranes; the oral and conjunctival areas will also show a bluish cast. Depending on the duration of hemolysis, bilirubin pigments may become deposited in the developing deciduous teeth. As these teeth erupt, they show a yellowish-green discoloration of the dentin, which is most obvious on the root surfaces.

LABORATORY FINDINGS

The hemoglobin, hematocrit, and red blood cell count are markedly decreased, and unconjugated bilirubin is significantly increased. The disease can be detected in utero by assessing a Coombs test of the mother's blood. This is an assay that detects maternal antibodies to the infant's erythrocytes.

TREATMENT

On delivery, the cyanotic neonate is subjected to rapid diagnostic tests; when fetal erythroblastosis is confirmed, blood transfusions are initiated. Once the maternal antibodies have been cleared from the infant's serum, the hemolysis will cease. Failure to act quickly may result in mental retardation or even death.

WHITE BLOOD CELLS

Leukocytes are formed within the bone marrow and are derived from partially differentiated stem cells. The neutrophil and monocyte are derived from a common precursor of the myelogenous series. The mononuclear cells derived from lymphoblasts differentiate into T and B subsets. Lymphoid stem cells reside in the marrow, lymph nodes, and the spleen. Factors that influence the bone

marrow may have a deleterious effect on leukocyte histogenesis. A variety of chemicals and cytotoxic agents will inhibit mitosis of the formative leukocytes. When other pathologic processes crowd out the leukocyte blast cells (myelophthisic response), the total circulating white blood cells will decrease. In addition, other processes in which the cause is unknown can result in defective leukocyte maturation. Conversely, a number of leukocyte proliferative responses exist that will increase the number of circulating white blood cells. Both inflammatory and neoplastic disorders of white blood cells fall into this group.

The most commonly used indicator of leukocyte disease is the peripheral white blood cell count. The normal count in adults is 6000 to 9000 white blood cells/mm³ of

blood. The most prevalent circulating white cell is the neutrophil, followed by the lymphocyte; other circulating cells, including eosinophils, basophils, and monocytes, are usually present in low numbers. An increase in the total circulating white blood cell count is referred to as *leukocytosis* and a decrease is *leukopenia*. Although a leukocytosis may be caused by an increase in all types of leukocytes; more commonly, an absolute increase or decrease in a specific subpopulation of leukocytes accounts for the elevated white blood cell count. Therefore it becomes important to know the absolute numbers of each type of leukocyte or to compare the relative proportions of each on a differential white cell count. A leukocytosis may be seen in both leukemia and infection (Figure 12-6). In

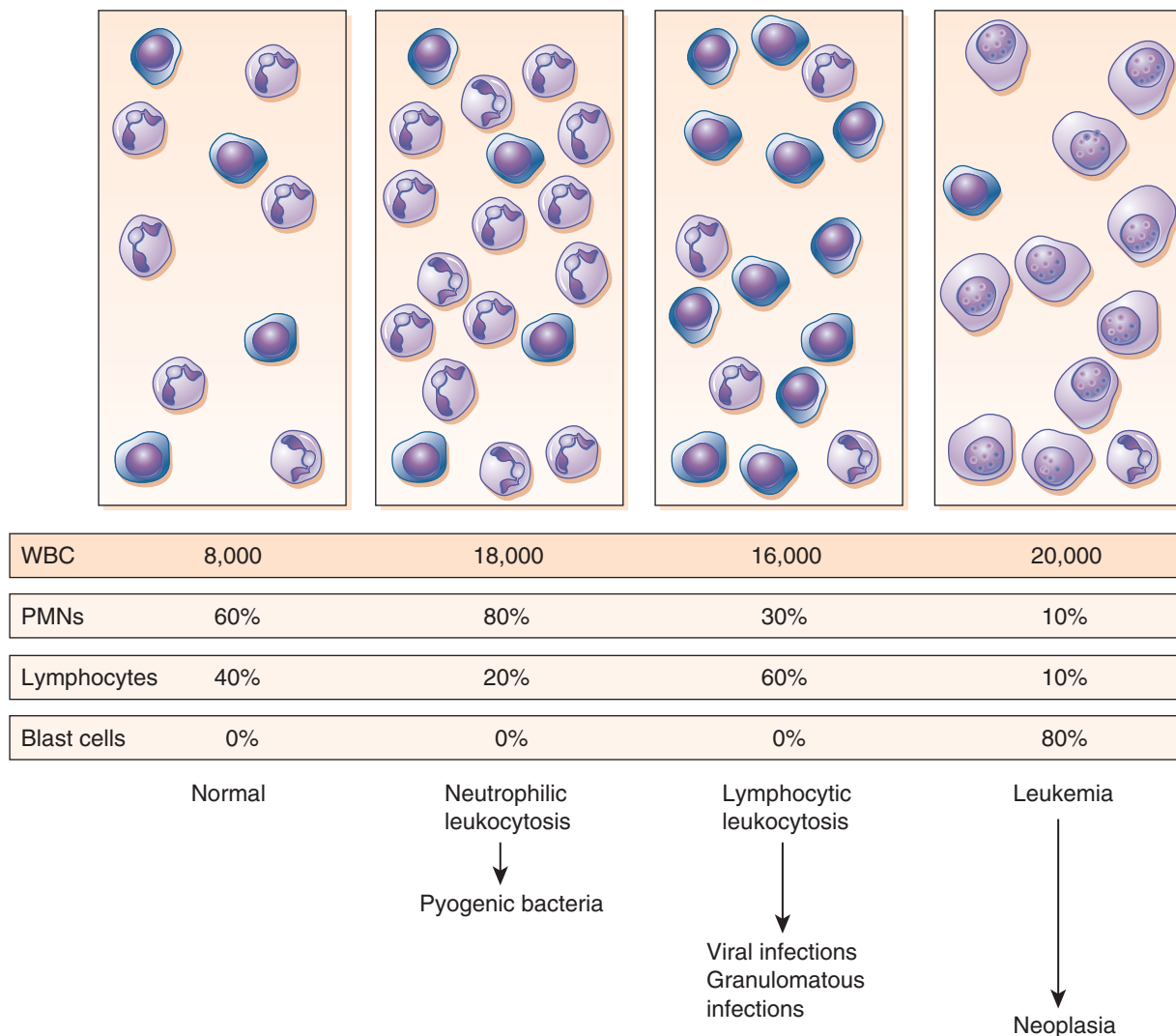


FIGURE 12-6

Leukocytosis. The total white blood cell count is elevated in infection (bacterial and viral) and leukemia. Pyogenic bacteria cause a neutrophilic leukocytosis, whereas viral and some chronic bacterial and fungal granulomatous infections induce a lymphocytic leukocytosis. In leukemia the differential white blood cell count will show primitive malignant blast cells. PMNs, polymorphonuclear leukocytes; WBC, white blood cells.

inflammatory responses caused by infections, the white cells retain their differentiated morphologic appearance while the total number simply increases. In leukemia the immature malignant cells leave the bone marrow before being fully differentiated, and therefore blast cells are encountered in unusually high numbers within the peripheral blood.

LEUKOPENIA

Although leukopenias may be associated with an overall reduction in leukocytes, they are most commonly associated with a decreased ability to generate neutrophils. Therefore the most common form of leukopenia is agranulocytosis or neutropenia. Lymphopenia may be encountered but is rare. A decrease in circulating leukocytes implies that (1) there has been an arrest of the maturation of the cells of the bone marrow, (2) the hematopoietic elements have been replaced, or (3) pharmacologic agents have inhibited cell cycling.

Agranulocytosis

AGRANULOCYTOSIS: A marked decrease in circulating granulocytes, particularly neutrophils, attributable to a variety of causes.

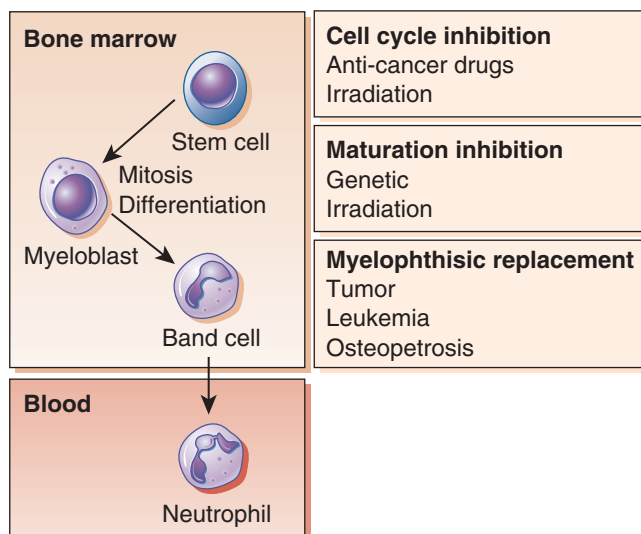


FIGURE 12-7

Agranulocytosis. Mature neutrophils circulating in the blood stream arise from stem cells of the marrow that undergo prior mitosis and differentiate into myeloblasts and band cells. A decrease in circulating neutrophils can be the consequence of mitotic inhibition, failure of cells to mature, or increased osteogenesis in the marrow compartment (osteopetrosis).

Agranulocytosis implies a total or absolute deficiency in the number of granulocytes. In practice the term actually refers to a decrease in polymorphonuclear leukocytes or neutrophils (neutropenia) (Figure 12-7). The most common cause of agranulocytosis is cancer chemotherapeutic agents that arrest the cell cycle or interfere with the assembly of the mitotic spindle. In these instances other hematopoietic cells may be decreased, including erythrocytes and thrombocytes. An additional common cause of agranulocytosis is leukemia. As the bone marrow becomes overpopulated with malignant leukocytes, normal hematopoiesis can no longer proceed because of the encroachment. In this ironic situation a leukocytosis exists, represented by high numbers of circulating malignant blast cells yet leukopenia of the normal blood elements exists. Because all of these cells are affected, agranulocytosis is usually coexistent with anemia and thrombocytopenia.

An idiopathic form of agranulocytosis is seen in which neutrophils fail to mature at the required physiologic rate. The **myelodysplastic syndrome** is one such condition; in many cases it represents an early form of myelogenous leukemia whereby the patient remains leukopenic for many years before a leukemic episode evolves.

CLINICAL FEATURES

Because neutrophils are the main cellular line of defense against bacterial infections, agranulocytosis, if severe, can result in death because of secondary bacterial infection. Although these infections can involve any organ, bacterial pneumonia is a frequently encountered complication.

Oral ulceration becomes a prominent finding when cancer chemotherapeutic drugs reach a toxic



FIGURE 12-8

Agranulocytosis. Agranulocytic ulceration of the gingiva and buccal mucosa.

threshold and the white cell count precipitously drops (Figure 12-8). The breakdown in oral epithelium is probably the result of direct toxic drug effects on these cells. The ulcers may resemble the common aphthous ulcer and can be located anywhere within the oral mucous membrane. In other cases the ulcers are much larger and irregularly shaped. Within a few days the ulcerations continue to enlarge and extend down to the bone with resultant osteomyelitis and sequestration. When deep ulcers are encountered in agranulocytosis, the prognosis is extremely grave and a life-threatening infection is imminent.

LABORATORY FINDINGS

In agranulocytosis the total white blood cell count becomes greatly decreased and may be as low as 1000 cells/mm³. The differential count will reveal an absolute decrease in circulating neutrophils. The normal levels of 60% to 65% neutrophils may drop to 10% to 15%. When associated with myelodysplastic syndrome or an early phase of full-blown leukemia, atypical blast cells should be evident on a peripheral blood smear. Bone marrow aspiration will determine which cells are neoplastic within the marrow.

Biopsy of an oral ulcer shows pathognomonic findings. The surface epithelium is ulcerated and replaced by a fibrin clot. Unlike most ulcerations that show leukocytic infiltration into the zone of ulceration, the agranulocytic ulcer is devoid of neutrophils.

TREATMENT

In acute agranulocytosis secondary to chemotherapy, the drug regimen should be immediately adjusted to avoid secondary and severe infection. Antibiotic therapy may be indicated, and transfusion with leukocytes should be considered. Recombinant leukocyte growth factors such as the granulocyte-monocyte colony-stimulating factor may be used in immunosuppressed patients with agranulocytosis. Before treatment can commence, the cause for the agranulocytosis must be identified. Agranulocytosis secondary to leukemia must be managed by chemotherapeutic approaches that inhibit or eliminate the neoplastic leukocytes. Paradoxically, these same medications may also inhibit neutrophil production. Bone marrow transplantation is often curative.

Cyclic Neutropenia

CYCLIC NEUTROPENIA: *An idiopathic disease in which episodic defects in neutrophil maturation in the bone marrow result in periodic decreases in circulating neutrophils.*

Cyclic neutropenia is a rare condition that is characterized by an episodic fluctuation in the number of cir-

culating neutrophils and is due to a bone marrow maturation arrest that occurs on a periodic basis. A germ line mutation in neutrophil elastase and other neutropenia genes has been discovered. In most patients the cycle occurs every 30 days with a neutropenic phase that persists for 4 to 5 days. Otherwise the number of circulating neutrophils in the interim is within normal levels.

CLINICAL FEATURES

Children with cyclic neutropenia suffer from frequent recurrent respiratory tract infections, which are usually bacterial in origin. On a regular basis they may develop short-term fevers that spontaneously resolve once the neutrophil count returns to normal. Within a few days of the neutropenic phase, aphthouslike oral ulcerations may appear and persist for 2 to 3 days. These ulcerations may arise on either fixed or movable mucosa. In addition, premature periodontal disease is often encountered, and children and teenagers may experience alveolar bone loss and periodontal pockets. Periodontal abscesses are rarely encountered, probably because the neutrophil count returns to normal levels in a short period.

LABORATORY FINDINGS

The total white blood cell count may decrease to 3000 cells/mm³ each month for a 5-day period. In the interim the white cell count approaches normal levels yet is usually slightly depressed. Therefore the clinician makes the diagnosis by obtaining weekly leukocyte counts over a 6-week period. The ulcers will show a decrease or absence of infiltrating neutrophils. The periodontal findings are histologically no different from those encountered in ordinary chronic inflammatory periodontal disease.

TREATMENT

Treatment with granulocyte-colony-stimulating factor (G-CSF) is effective. Patients with a tendency for more severe infections may be placed on recombinant G-CSF.

NEUTROPHIL FUNCTION DISORDERS

Neutrophils exert their defensive role against infectious agents by functioning as phagocytes and by exercising various intracellular mechanisms of microbial killing that include the elaboration of myeloperoxidase, lysosomal enzymes, and other cytoplasmic and microsomal antimicrobial peptides. Inherited defects in neutrophil function are rare but when present predispose patients to unchecked infection by certain microorganisms. Although the disease entity *chronic granulomatous disease of childhood* is the most common of these functional defects, other rare functional deficiencies, including *glucose-6-phosphate dehydrogenase deficiency*, *myeloperoxidase deficiency*, and the *lazy leukocyte*

syndrome, show similar clinical features. Oral mucosal infections can be seen in all of these diseases. Specific microbicidal, motility, and phagocytic function tests can be performed on blood samples taken from patients with suspected neutrophil function defects. Acquired functional defects can occur with drug administration, particularly corticosteroids.

Chronic Granulomatous Disease of Childhood

CHRONIC GRANULOMATOUS DISEASE

OF CHILDHOOD: An inherited disorder of neutrophil and monocyte function that predisposes patients to opportunistic infections.

Inherited as an X-linked disorder, chronic granulomatous disease of childhood represents a disease in which neutrophil microbicidal activity is defective. Various forms of the disease exist, all of which involve a suboptimal respiratory burst in the neutrophils and monocytes; the consequences are a lack of free radical formation and decreased peroxide and superoxide release. The various forms of the disease all involve defects in the electron transport enzyme and coenzyme pathways.

CLINICAL FEATURES

The disease evolves early in life with symptoms usually observed in children by age 2. It is characterized by susceptibility to a variety of opportunistic bacterial and fungal infections, including *Staphylococcus*, *Streptococcus*, the coliform microorganisms, and *Candida*. Clinically, draining lymphadenitis, hepatosplenomegaly, abscesses, pneumonia, and osteomyelitis are evident. Males are affected in the X-linked variant, and females act as carriers. The oral mucosa is often infected with *Candida* in which white pseudomembranous and erythematous lesions may be encountered anywhere in the mouth; the tongue, soft palate, and buccal mucosa are the most frequently affected sites. An eczematous cheilitis is often present along with facial skin lesions. Cervical lymphadenitis is invariably detectable, and drainage may be seen. Generalized ulcerative stomatitis, acute gingivitis, and advanced periodontitis are also common manifestations of the disease.

LABORATORY FINDINGS

A variety of function tests can be performed. The most widely available test is the quantitative nitroblue tetrazolium test. This test uses a redox dye that is sensitive to neutrophil respiratory activity. The test is negative in affected patients yet is normal or slightly reduced in female carriers. Tests that show defects in leukocyte microbicidal activity are also used in the diagnosis.

Usually a **neutrophilic leukocytosis** is seen, and hypergammaglobulinemia is detected. Biopsy of the oral mucosa in patients who develop candidiasis will disclose the presence of hyphae and yeast forms colonizing the superficial layers of the epithelium.

TREATMENT

The therapeutic aim is to prevent or contain life-threatening infection. Combination antibiotic therapy is usually required, and abscesses should be cultured to assess antibiotic sensitivity. Antifungal therapy should be prescribed when oral candidiasis is present. Delta interferon, which increases the leukocyte respiratory burst, and continuous sulfisoxazole therapy have also been used. Myeloablative conditioning with subsequent stem cell transplantation can be very effective when an identical human leukocyte antigen (HLA) match can be found.

LEUKOCYTOSIS

In this section, leukocytosis refers to disorders that evolve as a consequence of infectious diseases (Figure 12-9). An increase in circulating white blood cells occurring as a consequence of leukemia is discussed later. Because the

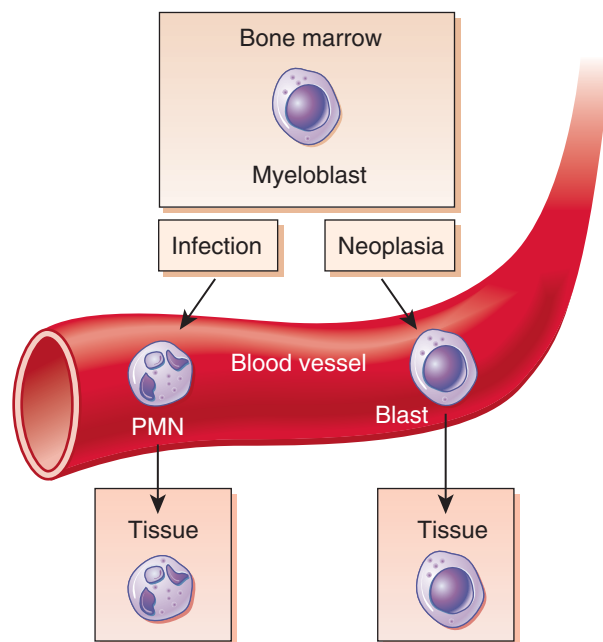


FIGURE 12-9

Leukocytosis versus leukemia. The myeloblast is stimulated to generate increased numbers of mature neutrophils (PMN) into the circulation in defense against pyogenic organisms (left). In myelogenous leukemia, increased numbers of immature (blastic) neutrophils enter the circulating blood as the result of neoplastic change in the myeloblast (right). PMN, polymorphonuclear leukocytes.

blood leukocytes are critical cellular elements in the defense against infectious disease, they increase their numbers when an active infection exists. The total circulating white blood cells increase above 10,000 during active infection. Neutrophilic leukocytosis evolves in response to pyogenic bacterial organisms such as *Streptococcus*, *Staphylococcus*, *Neisseria*, *Actinomyces*, and *Bacteroides*. **Mononuclear leukocytosis** may involve lymphocytes, monocytes, or both. Because lymphocytes and monocytes are active defense elements against viral infections, mononuclear leukocytoses are usually indicative of a viral infection.

Bacteria-Associated Leukocytosis

BACTERIA-ASSOCIATED LEUKOCYTOSIS: A marked elevation in levels of circulating neutrophils occurring as a result of an infection by pyogenic bacteria.

Pyogenic bacteria will initiate a neutrophilic leukocytosis and the white blood cell count will be elevated. A marked increase in mature neutrophils is seen, approaching 85%, on the differential count. As the marrow releases neutrophils into the circulating blood, some immature forms will be found to exit the marrow prematurely. Specifically, nonlobulated nuclei are encountered, and these immature neutrophils are termed **band cells**. The appearance of immature neutrophil forms may include earlier precursors such as metamyelocytes. A neutrophilic leukocytosis with immature neutrophils is referred to as a *shift to the left*. This term refers to the traditional diagrams of cellular maturation whereby the immature forms are illustrated on the left with arrows showing differentiation and maturation proceeding to the right. Therefore a shift to the left indicates a retrogressive phenomenon with appearance of immature, less differentiated cells.

CLINICAL FEATURES

Although an infection of any organ by pyogenic bacteria may induce a neutrophilic leukocytosis, it is important to realize that odontogenic and periodontal infections are bacterial and will cause the same type of reaction. Constitutional signs and symptoms of infectious diseases, including malaise and fever, will usually accompany the neutrophilic leukocytosis (see Chapter 3).

LABORATORY FINDINGS

Mononuclear leukocytosis is occasionally noted in nonpyogenic, specific bacterial and fungal infections that induce chronic granulomatous inflammation. In tuberculosis and deep fungal infections, oral ulcerations may be encountered and are usually deep seated with rolled margins. Granulomatous oral ulcers simply represent dissemination from a systemic infection that is usually of pulmonary origin.

TREATMENT

Leukocytosis of a reactive nature resolves once the infection has cleared. After resolution of the infection, the white blood cell count will usually return to normal levels within 1 to 2 days. Once the site of infection has been uncovered, culture and sensitivity are required to select the appropriate antibiotic. In the facial area, if the leukocytosis is associated with a soft tissue abscess, incision and drainage (I&D) may accelerate resolution. Alternatively, cellulitis, a more diffuse process, is not amenable to I&D.

Virus-Associated Leukocytosis

VIRUS-ASSOCIATED LEUKOCYTOSIS: A marked elevation in circulating lymphocytes and monocytes in response to a viral infection.

Viruses, being intracellular parasites, elicit a defense response in which the inflammatory cells are predominantly lymphocytes and monocytes; neutrophils play a very small role in the elimination of viral agents. Therefore the leukocytoses that accompany viral infections are typically mononuclear in nature and include small lymphocytes, large lymphocytes, and monocytes. Although the prototype viral infection with a mononuclear leukocytosis is infectious mononucleosis, most other viral infections will be associated with an increase in the lymphocyte count as well (see Chapter 7). Those caused by the herpes simplex virus, varicella-zoster virus, and coxsackievirus manifest oral and facial vesicles that ultimately ulcerate, contributing to the intensity of the inflammatory response.

Infectious Mononucleosis

INFECTIOUS MONONUCLEOSIS: An infectious disease of B lymphocytes caused by the Epstein-Barr virus (EBV) that produces a marked mononuclear leukocytosis.

The EBV possesses envelope molecules that bind to a B-lymphocyte receptor. Infected B lymphocytes rapidly proliferate in response to the infection by the EBV, thereby causing a mononuclear leukocytosis.

CLINICAL FEATURES

Infectious mononucleosis is acquired through droplets and aerosol or direct contact, accounting for the term *kissing disease*. After exposure and an incubation period of 7 to 10 days, the patient begins to experience fever and weakness. This malaise might be quite severe, restricting the patient to bed. As the symptoms progress, lymphadenopathy becomes a prominent finding, with the most severely affected nodes being the cervical, axillary, and inguinal. Enlarged tender swellings may be

identified at the angle of the mandible and down the cervical chain. The infection primarily affects young adults and children. An oral manifestation, which is not invariably present, is the appearance of petechiae in the soft palate. Although minor abnormalities in platelet function have been reported, the petechiae are probably induced by suction when the patient clicks a sore or itchy soft palate against the tongue. The disease usually persists for approximately 2 weeks and then spontaneously resolves. The virus has also been linked to the chronic fatigue syndrome that affects adults, primarily females. The association between chronic fatigue syndrome and a chronic latent EBV infection is tenuous.

LABORATORY FINDINGS

The white blood cell count may range from 15,000 to 20,000 cells/mm³, with a marked increase in lymphocytes and monocytes. On the differential smear, many of the lymphocytes appear to have undergone blastogenesis and appear atypical. These characteristically large lymphocytes are referred to as *Downey cells*, or simply *atypical lymphocytes*. A rapid serologic assay is the Monospot test, which detects antibodies to the EBV. A more specific quantitative assay is the heterophile antibody, or Paul-Bunnell test. Other specific antibodies to various components of the EBV coat can be detected in the serum, including the EBV early antigen (EA) and viral capsid antigen (VCA). Lymph node biopsy shows follicular hyperplasia with the appearance of many large reactive follicular center cell lymphocytes.

TREATMENT

No specific treatment exists for infectious mononucleosis, although the virus, which is a herpes group virus, will respond to systemically administered acyclovir. Treatment, however, does not usually speed resolution. General palliative care is recommended, including bed rest, adequate nutrition, and administration of analgesics.

NEOPLASMS

Neoplastic processes of leukocytes result in an elevation of the white blood cell count. These leukocytoses are referred to as the *leukemias*. Because leukocyte progenitors lie within the bone marrow and lymph nodes, other nonleukemic forms of malignant leukocyte neoplasia may cause widespread osteolytic disease or lymph node swelling, respectively. The most common leukocyte bone marrow malignancy is multiple myeloma, a neoplastic proliferation of B lymphocytes. Neoplastic lymphoid tumors associated with node enlargements are collectively referred to as the *lymphomas*. Although T cells may undergo neoplastic transformation, most lymphomas are of B-cell origin (Figure 12-10).

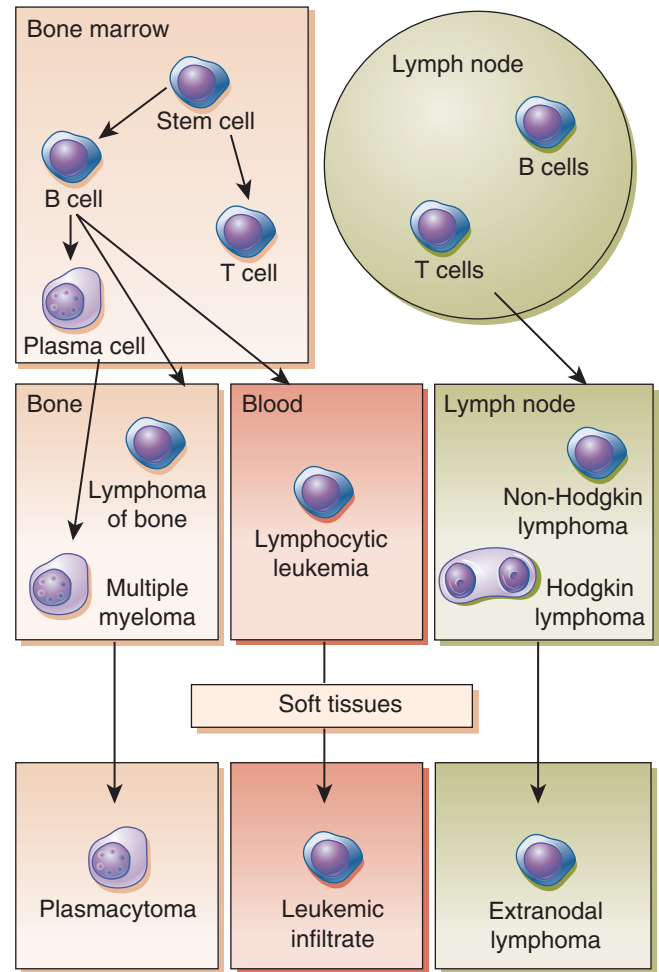


FIGURE 12-10

Lymphocyte malignancies. Lymphoid cells are generated in the bone marrow and in the lymph nodes. Bone marrow malignancies may take the form of leukemia or, within bone, lymphoma and plasma cell tumors (myeloma). Malignancies of lymph nodes may be either Hodgkin or non-Hodgkin lymphomas. All of these malignancies may infiltrate the soft tissue and, with the exception of leukemia, may arise in the soft tissue.

Leukemia

LEUKEMIA: Circulating malignant leukocytes of bone marrow or lymph node origin.

The leukemias are classified according to the specific leukocytic stem cell of origin. In this regard they are usually categorized in the granulocytic series, *myelogenous* or *granulocytic leukemia*, and in the lymphoid series, *lymphocytic leukemia*. Most leukemias among animals are caused by retroviruses. Although one form of leukemia, endemic to Japan, is associated with human T-cell lymphotropic virus type I, most leukemias in humans have not been definitively associated with a viral agent.

Oncogene mutations and overexpression are implicated in the pathogenesis of leukemias. In 80% of patients with chronic myelogenous (granulocytic) leukemia, a chromosomal translocation is observed between chromosomes 9 and 22 and is commonly referred to as the *Philadelphia chromosome* (t[9:22]). This translocation causes a juxtaposition of the *c-abl* proto-oncogene from chromosome 9 to a breakpoint cluster region on chromosome 22 (*bcr*). The resultant translocated and hybrid oncogene is implicated in the mechanism of carcinogenesis. Many other chromosomal abnormalities and oncogenes have recently been identified and associated with the various forms of human leukemia.

Another commonly used classification is based on the severity of the leukemia, regardless of the cell type. *Acute leukemias* are rapidly progressing, usually fatal, and tend to occur in children. The *chronic leukemias* are more often encountered among adults; although they are potentially fatal, many will undergo prolonged periods of remission with appropriate multidrug chemotherapy.

CLINICAL FEATURES

One of the earliest signs of leukemia is chronic fatigue and malaise. Because of a myelophthitic response in the bone marrow, as malignant leukocytes crowd out the other hematopoietic precursors, a tendency for petechial hemorrhages secondary to thrombocytopenia evolves. Anemia is also frequently encountered in leukemia. In addition to generalized malaise, the patient may develop fevers of unknown origin or other identifiable infections of the upper respiratory or genitourinary tracts. Within the oral cavity, petechial hemorrhages may also be identifiable. In both acute and chronic leukemias, gingival enlargement is encountered in 10% of untreated patients (Figure 12-11). Because the leukemic leukocytes are nonfunctional, all patients with leukemia are considered to be immunocompromised and are therefore susceptible to a variety of infectious diseases. Of major importance in dental practice is the propensity for a hemorrhagic diathesis because of the inability of platelets to be produced in the neoplastic bone marrow (myelophthitic thrombocytopenia).

LABORATORY FINDINGS

In leukemia the white count may fluctuate widely, varying from no increase in white cells or even a leukopenia to that of a marked leukocytosis. The differential smear, however, will usually disclose the presence of blast cells, even in the leukopenic phase of leukemia (the so-called *aleukemic leukemia* phase). Invariably a pronounced leukocytosis soon occurs as the malignant cells emanating from the marrow begin entering the circulating blood at a rapid pace. The leukocytosis of leukemia is easily differentiated from that of infection because of the appearance of large numbers of blast cells in the peripheral smear. Bone marrow aspiration is usually performed to specifically



FIGURE 12-11

Leukemia. **A,** Generalized gingival swelling and erythema as an early clinical manifestation of acute myelogenous leukemia in a child. **B,** Ulcerated mass representing a localized leukemic infiltrate of myelogenous cells (granulocytic sarcoma) in a young adult. (**A** Courtesy Dr. Donald Duperon.)

identify the cell type or lineage of the blast cells. Immunocytochemical markers and flow cytometry are often used to refine the diagnosis. The diagnostic precision of immunomarkers and cytometry is of clinical importance, because specific precursor cells respond differently to the various array of available chemotherapeutic agents.

HISTOPATHOLOGY

Biopsy of the enlarged gingiva will disclose the presence of a leukemic infiltrate. Separation from an inflammatory gingival hyperplasia is made by the presence of

mononuclear blast cells that show cytologic atypia. Specific immunocytochemical markers are necessary to ascertain whether the cells are of myelogenous or lymphocytic duration (Figure 12-12). Some forms of myelogenous leukemia are notorious for producing soft tissue infiltrates that can become quite large. Specifically, **granulocytic sarcoma** is a tumor mass that occurs when leukemic cells infiltrate the soft tissue in myelogenous leukemia. These cells can be identified using enzyme histochemistry, because they are chloracetate esterase positive.

TREATMENT

The treatment for leukemia is tailored according to the specific diagnosis, which is based on the cell of origin, degree of differentiation, and severity of disease. In general, most forms of leukemia are managed by multidrug regimens, which are used until a remission evolves. Sometimes remissions last many months or even years before repeated chemotherapy is required. In intractable refractory leukemias the option for bone marrow transplantation is available. In these instances high-potency cytotoxic drugs are combined with total body irradiation to eradicate all malignant cells. Donor marrow is then grafted into the recipient. **Graft-versus-host disease (GVHD)** is a predictable complication that must be controlled by the administration of such immunosuppressive drugs as steroids and cyclosporine. Because gingival enlargement is the consequence of leukemic cell infiltration, it will resolve as the patient responds to chemotherapy. If cyclosporine is used as the therapeutic agent, a gingival enlargement may again ensue because of medication-induced fibrosis rather than malignant cell infiltration. A platelet count should be assessed in all patients with leukemia before performing oral surgery.

Hodgkin Lymphoma

HODGKIN LYMPHOMA: A malignant tumor of lymphocytes characterized by the appearance of Reed-Sternberg cells.

Hodgkin lymphoma is a malignancy of a specific type of lymphoid precursor cell that is not completely understood. The cell is referred to as the *Reed-Sternberg* cell and exhibits a specific morphology that is identifiable on lymph node biopsies of patients with Hodgkin lymphoma. Four subtypes are classified according to the variations in the lymphocyte cell population when observed microscopically (Table 12-1). Each of these subtypes conveys a unique prognosis. In addition to the histologic subtyping, all lymphomas are subjected to clinical staging (Table 12-2).

Stage 1 disease is characterized by involvement of a single group of lymph nodes in a given anatomic area, whereas stage 2 disease represents nodal involvement in more than one region. Stage 3 disease includes lymphoid involvement above and below the diaphragm, whereas stage 4 is reached when the malignant cells are disseminated and are no longer confined to lymphoid tissue. Stage 1 lymphoma, regardless of the histopathologic

Table 12-1 Classification of Hodgkin Lymphoma

Histologic Type	Prognosis	Five-Year Survival Rate
Lymphocyte predominance	Very good	90%
Nodular sclerosis	Good	70%
Mixed cellularity	Fair	60%
Lymphocyte depletion	Poor	20%

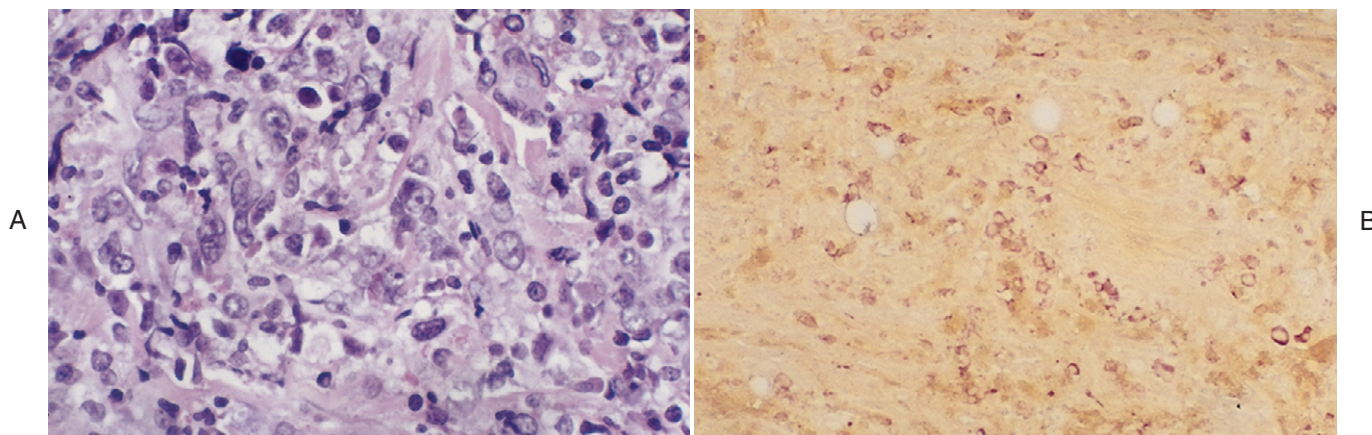


FIGURE 12-12

Leukemia. **A**, Atypical leukocyte blast cells infiltrating the connective tissue. **B**, Specific immunomarker for myeloid cells in the infiltrate indicates the patient has a myelogenous leukemia (granulocytic sarcoma).

type, has a relatively good prognosis when appropriate therapy is selected, whereas stage 4 disease has a dire prognosis (most patients succumb to the disease regardless of treatment). The same clinical staging system applies to non-Hodgkin lymphomas.

CLINICAL FEATURES

Hodgkin lymphoma is more common among males than females and has a predilection for the third decade of life. Hodgkin lymphoma begins in a single lymph node that becomes progressively enlarged and may be firm or rub-

bery on palpation. The cervical chain of lymph nodes is a common site for Hodgkin lymphoma; axillary and inguinal node groups may also be the initial sites. Patients often experience low-grade episodic fever and night sweats. With advancing stages of the disease, additional node groups may be palpable and splenomegaly may be detected. The nodes of advanced disease are often multiple and confluent with a matted character. Because most lymph node enlargements are inflammatory in nature, it is important to realize that the early phases of Hodgkin disease may simulate an inflammatory process. When no infectious source can be identified and the affected node persists for over 1 month, fine-needle aspiration cytology should be undertaken.

Hodgkin disease rarely occurs as an extranodal process and is therefore not identified within the soft tissue of the oral cavity. Only in widely disseminated stage 4 disease might a tumor deposit be identified in the oral soft tissue or within the jaws.

Table 12-2 Clinical Staging of Lymphoma

Stage	Extent of Disease
1	Single node region or single extranodal site
2	Two or more nodes localized on one side of diaphragm
2 _E	Same as in 2, with contiguous extranodal extension
3	Nodes on both sides of diaphragm involved
3 _S	Same as 3, including spleen
3 _E	Same as 3, with contiguous extranodal extension
4	Disseminated disease with extranodal, noncontiguous tumor

HISTOPATHOLOGY

As mentioned previously, the diagnosis of Hodgkin disease is based on the presence of the Reed-Sternberg cell. This cell has a characteristic morphologic appearance; it is binucleated, sometimes multinucleated, with the nuclei round to oval and quite large (Figure 12-13). The

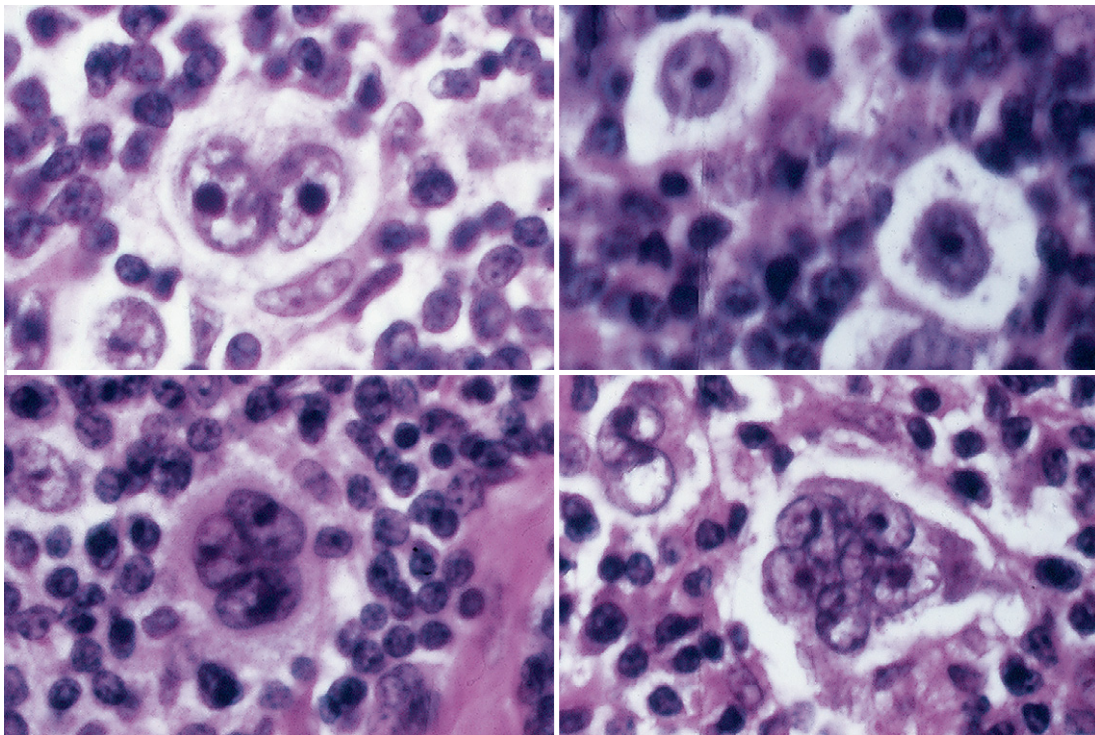


FIGURE 12-13

Hodgkin lymphoma. Four different appearances of the Reed-Sternberg cell that is diagnostic of this neoplasm. The classic “owl eyes” appearance is present in the upper-left photomicrograph.

nuclear membrane is prominently stained, and the nucleoplasm is quite pale with a prominent, centrally placed nucleolus. This binucleated cell resides within a vacuolated lacunar space separated from the remaining sheets of lymphoid cells. Four histopathologic classifications are based on the ratio of Reed-Sternberg cells to the associated lymphocytic population. Common to all Hodgkin lymphomas is effacement of the normal lymph node architecture with replacement of the germinal centers by diffuse sheets of lymphoid cells. The most favorable prognosis is associated with the

lymphocyte predominance type. Reed-Sternberg cells are widely dispersed and few in number. The neoplasm is dominated by diffuse sheets of relatively monomorphic-appearing lymphocytes, although some may have enlarged nuclei (Figure 12-14, A). Scattered Reed-Sternberg cells within their lacunae and a polymorphous leukocytic population characterizes the *mixed cellularity type*. Included in the mixed cell type are monocytoïd cells, lymphocytes, and numerous eosinophils (Figure 12-14, B). Large confluent multinodular aggregates of lymphocytes and intervening collagen

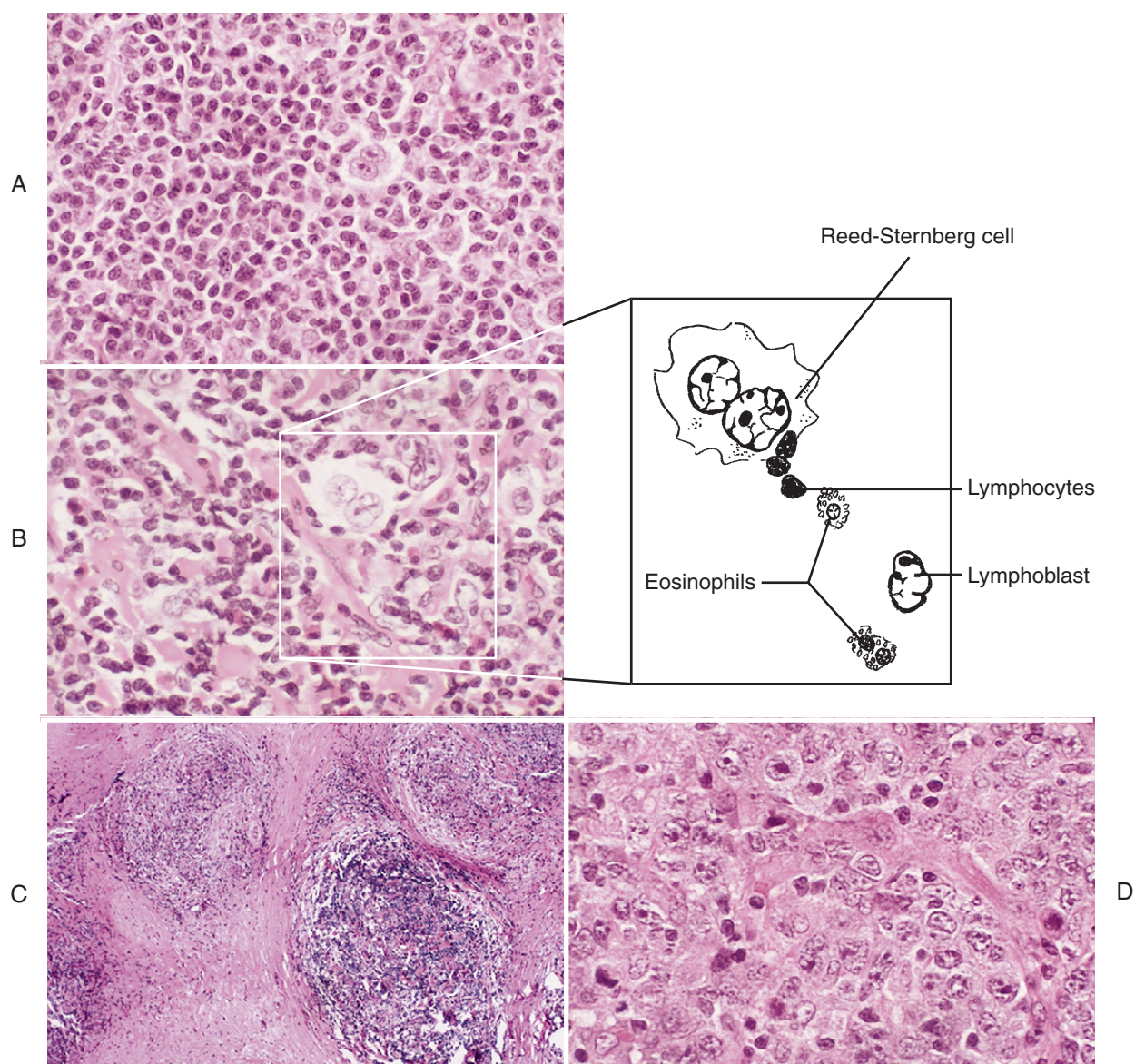


FIGURE 12-14

Hodgkin lymphoma. The appearance of the basic four histopathologic classifications of Hodgkin lymphoma. **A**, Lymphocyte predominance. **B**, Mixed cellularity. **C**, Nodular sclerosis. **D**, Lymphocyte depletion.

deposits characterize *nodular sclerosis*. Reed-Sternberg cells are present in greater numbers (Figure 12-14, C).

The worst prognosis is associated with the *lymphocyte depletion* variant of Hodgkin lymphoma. Reed-Sternberg cells dominate the microscopic fields with only scattered lymphocytes (Figure 12-14, D). In addition, large mononuclear lymphoblasts are identified that resemble the Reed-Sternberg cell by having a vesicular nucleoplasm with a prominent nucleolus. Mitotic figures are also commonly encountered.

TREATMENT

The treatment is based on the stage of disease and histomorphologic subtype. A stage 1 lymphocyte predominant Hodgkin lymphoma has an excellent prognosis, and most patients will survive the disease after radiotherapy and chemotherapy. Conversely, a stage 4 lymphocyte depletion type would carry the worst prognosis, and most individuals would not survive 12 months. Oncologists have selected and specified combination chemotherapeutic drugs for each type of Hodgkin lymphoma; radiation therapy plays a major role in the control of the disease.

Non-Hodgkin Lymphoma

NON-HODGKIN LYMPHOMA: A malignant neoplasm of lymphocytes lacking Reed-Sternberg cells.

Lymphomas characterized by diffuse or nodular sheets of lymphocytes or lymphoblasts without the presence of Reed-Sternberg cells are classified as non-Hodgkin lymphoma. These lymphomas are clinically staged in similar fashion to Hodgkin lymphoma. As a group they carry a worse prognosis. As with Hodgkin lymphomas the non-Hodgkin lymphomas are diagnosed according to the cell population that predominates. Denoting the subtypes is important, because all have different prognoses. The currently used histiopathologic classification is quite complex (Box 12-1), consisting of a combination of the Revised European—American Classification of Lymphoid Neoplasms (REAL) and the World Health Organization (WHO) classification. Although most non-Hodgkin lymphomas are derived from B lymphocytes, a cutaneous form that originates from T cells is encountered. This cutaneous T-cell lymphoma is extranodal and is referred to as **mycosis fungoides**. Rarely, cutaneous and lymphoid tissues are involved simultaneously, and the disease is referred to as the **Sézary syndrome**.

CLINICAL FEATURES

Non-Hodgkin lymphomas usually arise within lymph nodes; however, particularly within the oral cavity, extranodal disease is occasionally encountered. Indeed, those lymphomas associated with acquired immunodeficiency

syndrome (AIDS) are frequently extranodal in location, being encountered in such tissues as the brain, oral mucosa, and the gut. Non-Hodgkin lymphomas are more frequently encountered in males than females and tend to occur in an older age group than those with Hodgkin lymphoma. Most patients are in the fourth or fifth decades of life. The earliest sign is a lymph node enlargement that persists or progressively enlarges. Low-grade fever and night sweats are common symptoms.

In the head and neck regions, non-Hodgkin lymphoma will manifest as a firm or rubbery cervical node enlargement that persists for over 1 month without any diminution in size (Figure 12-15). Inguinal and axillary nodes may also be involved, as may the liver and spleen.

BOX 12-1

Updated REAL/WHO Classification (modified)*

B-CELL NEOPLASMS

Precursor B-cell neoplasm
 B-acute lymphoblastic leukemia/lymphoma
 Peripheral B-cell neoplasms
 B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma
 B-cell prolymphocytic leukemia
 Lymphoplasmacytic lymphoma
 Mantle cell lymphoma
 Follicular lymphoma
 Extranodal marginal zone B-cell lymphoma (MALT type)
 Nodal marginal zone B-cell lymphoma
 Splenic marginal zone lymphoma
 Hairy cell leukemia
 Plasmacytoma/plasma cell myeloma
 Diffuse large B-cell lymphoma
 Burkitt lymphoma

T-CELL AND PUTATIVE NK-CELL NEOPLASMS

Precursor T-cell neoplasm
 T-acute lymphoblastic leukemia/lymphoma
 Peripheral T-cell and NK-cell neoplasms
 T-cell chronic lymphocytic leukemia/prolymphocytic leukemia
 T-cell granular lymphocytic leukemia
 Mycosis fungoides/Sézary syndrome
 Peripheral T-cell lymphoma
 Hepatosplenic T-cell lymphoma
 Subcutaneous T-cell lymphoma
 Angioimmunoblastic T-cell lymphoma
 Extranodal T-cell/NK-cell lymphoma, nasal type
 Intestinal T-cell lymphoma
 Adult T-cell lymphoma/leukemia
 Anaplastic large cell lymphoma, systemic type
 Anaplastic large cell lymphoma, cutaneous type
 Aggressive NK-cell leukemia

*Includes circulating (leukemic) phase of lymphoid neoplasias.

**FIGURE 12-15**

Lymphoma. A common head and neck clinical presentation of multiple, coalesced, persistently enlarged, firm, rubbery lymph nodes in the cervical area.

In the later stages of disease, multiple node groups may be affected along with hepatosplenomegaly.

Extranodal lymphomas arising within the oral cavity can occur centrally in the jawbones or arise in the oral soft tissue. In primary lymphoma of bone, patients may complain of pain and paresthesia or simply note osseous enlargements, usually in the mandible. Radiographs will disclose an irregular, poorly margined radiolucency, and teeth in the affected area may show divergence or root resorption. Clinically the teeth in an affected area often become loose. Soft tissue involvement may be seen anywhere in the oral mucosa, being more often identified as an enlargement or swelling on the gingiva or on the palate.

In human immunodeficiency virus (HIV) infections, malignant lymphoma is the second most commonly encountered malignancy after Kaposi sarcoma; extranodal localization in the oral cavity is frequently observed and generally identified on the palatal gingiva (Figure 12-16). Intraosseous lymphomas of the jaws in AIDS patients are extremely rare. The oral tumors are usually ulcerated, exhibit a rapid growth rate, and are frequently tumefactive or fungating.

A specific form of non-Hodgkin lymphoma occurs in the facial region and is referred to as *malignant* or *polymorphous reticulosis*. The tumor has an affinity for the midline structures of the face and will proliferate in the region of the nasal septum, causing osteolytic change with invasion into the ethmoids and through the nasal floor and palate. These lesions may occasionally perforate through the palate, yielding a large necrotic mass within the oral cavity. These unique lymphomas are of-

**FIGURE 12-16**

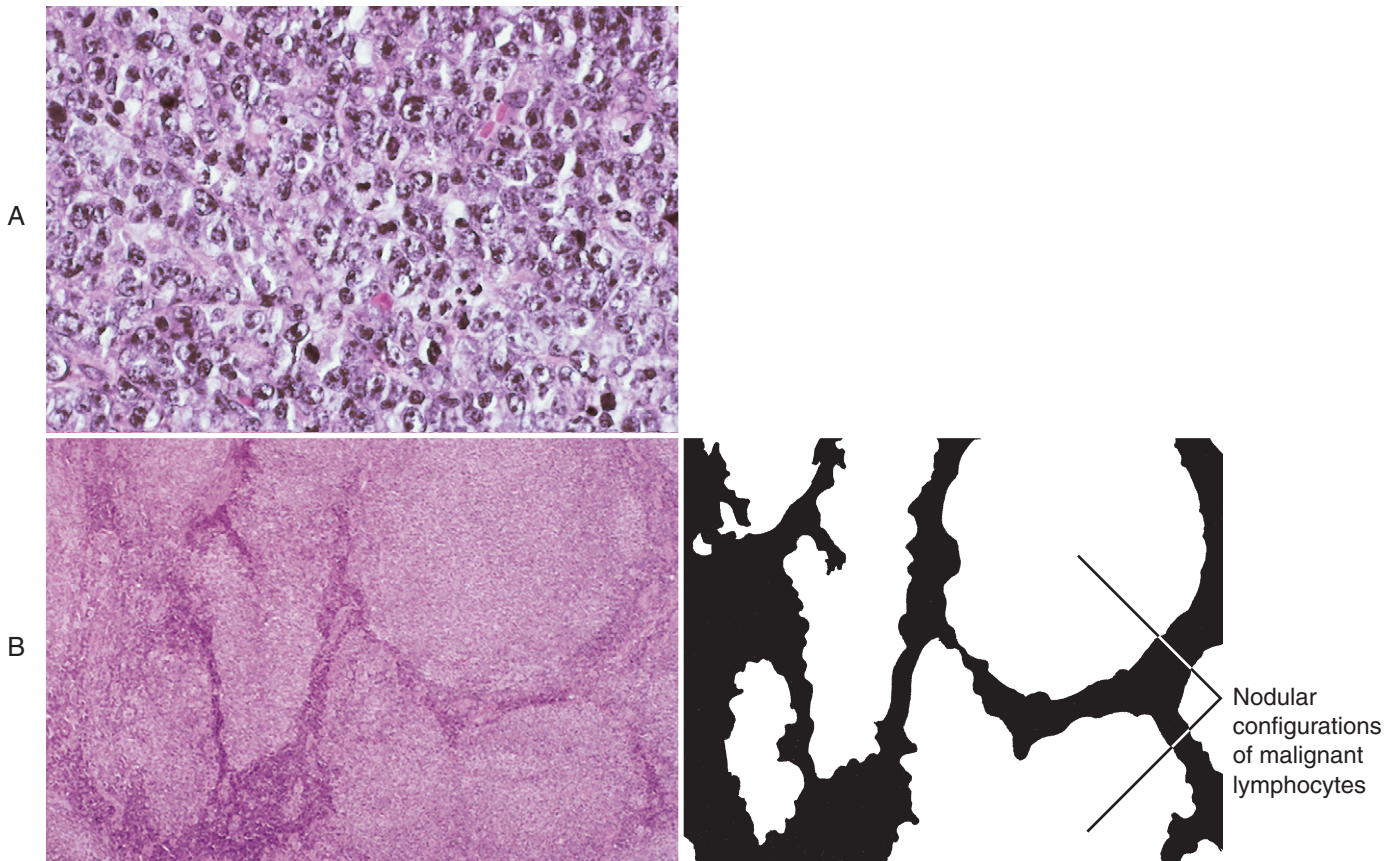
Lymphoma. HIV-associated lesion present on the gingiva and tuberosity.

ten of T-cell or Null cell origin. Similar clinical findings are encountered in Wegener granulomatosis or midline lethal granuloma, immunopathologic disorders characterized by vasculitis.

HISTOPATHOLOGY

In most forms of non-Hodgkin lymphoma the peripheral blood leukocyte count is normal. One form, diffuse lymphocytic lymphoma, is often associated with chronic lymphocytic leukemia, and therefore a leukocytosis with circulating leukemic blast cells will be encountered. Microscopically the normal lymph node architecture is destroyed, and malignant lymphocytes frequently invade the lymph node capsule. The affected node is significantly enlarged, and the growth pattern is divided into two major subcategories: (1) diffuse, in which sheets of lymphoid cells prevail, and (2) nodular, in which the malignant cells form confluent ovoid clusters that resemble markedly enlarged germinal centers (Figure 12-17). In nodular lymphomas, little or no intervening medullary lymphoid tissue exists. As a group the lymphomas with a nodular pattern carry a better prognosis than those that are diffuse.

The histopathologic subtyping is based on the differentiation of the lymphoid precursor cells; the more primitive, anaplastic tumors are high grade, and the more differentiated tumors, which bear a greater resemblance to mature lymphocytes, are low grade. A variety of cell surface markers, which are useful in these classification schemes, identify lymphoid cells at varying stages of maturation. Both classifications take into account the resemblance of B-cell lymphoma

**FIGURE 12-17**

Lymphoma. **A**, Atypical lymphocytes in diffuse form of non-Hodgkin lymphoma. **B**, Nodular pattern of proliferation in non-Hodgkin lymphoma.

populations to the B-cell region of the lymph node. The large-cell lymphomas emulate large follicular center cells or lymphoblasts. Intermediate-size cells with pale chromatin represent immunoblasts or lymphoblasts; and the well-differentiated cells are small and round, resembling mature lymphocytes. Most extranodal lymphomas occurring in AIDS are represented by intermediate-size lymphoblasts or large anaplastic blast cells. They are therefore high-grade lymphomas.

The cells identified in malignant polymorphous reticulosis are pleomorphic-appearing lymphocytoid cells. They range from small lymphocytes to large blast-appearing cells. Mitotic figures and pleomorphism are common, and the cells tend to surround blood vessels (**angiocentric lymphomas** and many are of T- or Null cell origin, the latter lacking markers for either B or T lymphocytes). Frequently, a significant amount of necrosis exists within the specimen, and the osseous trabeculae show osteoclastic resorption along the leading edge of the infiltrating tumor.

T-cell lymphomas associated with mycosis fungoides demonstrate characteristic histopathologic features on skin biopsy. The subcutaneous tissue is infiltrated diffusely with relatively monomorphic-appearing small lymphocytes, and clusters of lymphoid cells transigrate into the overlying epithelium, referred to as **Pautrier microabscess**. The diagnosis can usually be confirmed by using a monoclonal antibody to T-cell markers. The oral mucosa is rarely involved.

Polyclonality refers to the ability of a population of lymphoid cells to synthesize a mixture of light and heavy chain immunoglobulins, whereas *monoclonality* is used for a population of cells that can only produce either a single type of light chain or a heavy chain immunoglobulin. The pathologist is sometimes confronted with a lymphocytic infiltrate or a proliferative lesion in a lymph node in which the histologic features are ambiguous. Tests for clonality are important, because a monoclonal cell population occurs in malignancy, whereas polyclonal cells are most consistent with an inflammatory cell infiltrate.

Receptor gene rearrangement assays will disclose clonality in lymphoid lesions. The B-cell receptor is the immunoglobulin molecule, whereas T cells have a different type of receptor (Tcr). In diverse or polyclonal proliferations the B- and T-cell receptors normally evince a heterogeneous population of receptor gene rearrangements, because each receptor molecule binds a different and unique antigen. Alternatively, only a single species of rearranged receptor genes will be identified in a monoclonal malignant proliferation (Figure 12-18).

Gene rearrangement

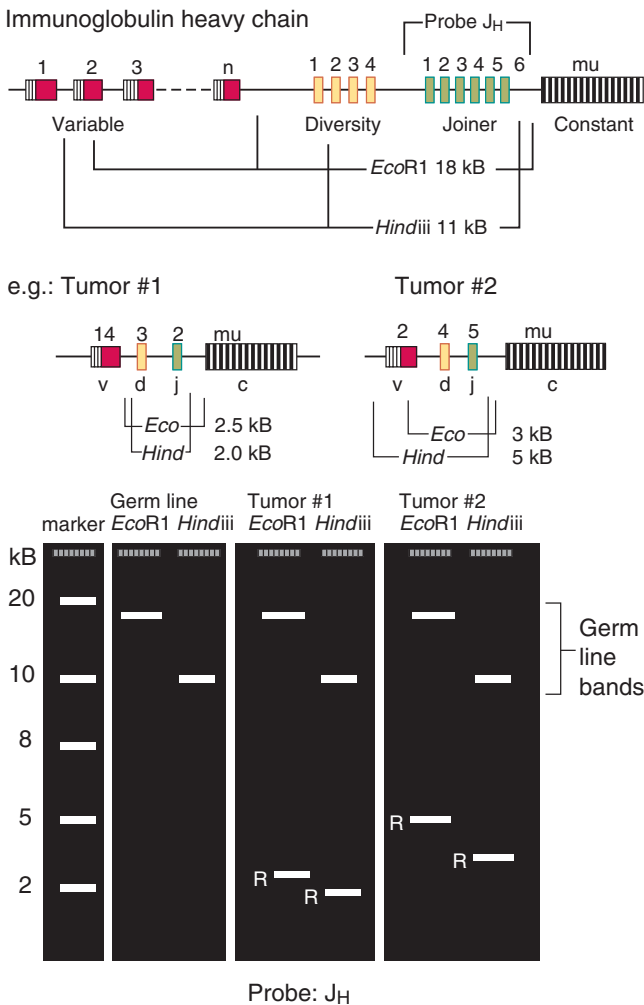


FIGURE 12-18

Lymphoma. The immunoglobulin gene is intact in nonlymphoid tissue. When DNA from normal cells is cut with restriction enzymes, a germ line pattern is seen on electrophoresis (column 2 bottom). In B-cell lymphomas, the immunoglobulin gene is rearranged identically in the malignant cells. This yields different length segments of DNA from the germ cell line bands derived from the normal cell population (columns 3 and 4).

TREATMENT

As with Hodgkin lymphoma the non-Hodgkin lymphomas are managed according to the stage of the disease and the histopathologic subtype. Multiregimented chemotherapy and radiation therapy are used.

MALT Lymphoma

MALT LYMPHOMA (MALTOMA): A variant of lymphoma that arises from mucosa-associated lymphoid tissue (MALT) that can be found throughout the digestive tract.

Throughout the digestive tract are lymphoid organs that are located in the submucosal connective tissues. They do not exist as lymph nodes; instead they are small aggregates of lymphoid cells that exhibit germinal centers. In the lower gastrointestinal (GI) tract these lymphoid organs are involved in IgA formation. In the head and neck area, MALT lymphomas typically arise from lymphoid aggregates that are located in the salivary glands. An outer mantle of lymphocytes and a more peripheral layer of lymphocytes (called the *marginal zone*) surround the germinal centers. It is this population of cells that is believed to be the origin for MALT lymphomas. Head and neck maltomas are primarily found in the parotid gland and in the palatal minor salivary tissue. The tumors in the parotid show a histologic resemblance to lymphoepithelial sialadenitis that accompanies Sjögren syndrome (SS).

The lymphoid infiltrates that occur in the palate are often referred to as *atypical lymphoproliferative disease*, because the pathologist is not always certain whether such infiltrates are a reactive inflammatory lesion (reactive lymphoid hyperplasia) or a low-grade lymphoma. In fact, follow-up studies have disclosed that even the reactive-appearing lesions can progress to lymphoma given time (months or even years after the original diagnosis), and atypical lymphoproliferative disease of the palate is best classified as a *maltoma*.

CLINICAL FEATURES

Maltomas of the parotid glands are most commonly seen in patients with SS; however, they may also arise de novo, without any preexisting parotid inflammatory disease. The involved gland may be either diffusely enlarged, or the tumor may appear as a discrete nodule that is either rubbery or firm to palpation. In SS, the neoplastic element derives from lymphocytes that populate the characteristic lymphoid infiltrate of the disease (lymphoepithelial sialadenitis). These cells develop as phenotypically identical clones of marginal zone lymphocytes.

Atypical lymphoproliferative disease of the palate is a unique lesion that may be clinically confused with a salivary tumor. As the lymphoid infiltration progresses, it causes a diffuse soft, fatty appearing mass of the hard and soft palate junction. This diffuse lesion is typically unilateral yet may extend past the midline. Patients have no symptoms of pain, paresthesia, or numbness.

HISTOPATHOLOGY

MALT lymphomas of the parotid gland are poorly demarcated lesions that under low magnification exhibit a pattern almost identical to lymphoepithelial sialadenitis as may be encountered in SS. Infiltrating lymphocytes surround epimyoepithelial islands (Figure 12-19, A and B). When the cells are examined under higher magnification, they are not merely small lymphocytes that are typically seen in lymphoepithelial sialadenitis; instead they are atypical with plasmacytoid and histiocytoid appearances, and the nuclei are larger than mature lymphocytes. The atypical cells tend to envelop the epimyoepithelial islands. CD20 positivity is encountered in these cells, confirming their B-cell differentiation (Figure 12-19, C).

In atypical lymphoproliferative disease of the palate, lymphocytes infiltrate the minor salivary gland parenchyma, obliterating the acini, yet the intralobular ducts are preserved. Only rarely are true epimyoepithelial islands encountered as in MALT lymphoma of the parotid gland. The lymphoid infiltrate may be diffuse or nodular. In the nodular form, the process may appear to represent a reactive inflammatory process but follow-up has shown that these patients may have lymphoma in other lymphoid organs synchronously or more widespread involvement may appear months or years later.

TREATMENT

In the gut, MALT lymphomas have been associated with *Helicobacter pylori* infection. This association in salivary maltomas has not been conclusively demonstrated. When compared with other non-Hodgkin lymphomas, MALT lymphomas have a much more favorable prognosis. Low-dose radiation therapy is effective for lymphoproliferative disease of the palate, and chemotherapeutic interventions are used in parotid disease. Importantly, an oncologic workup is essential to explore for dissemination of disease, particularly in the spleen and lymph nodes.

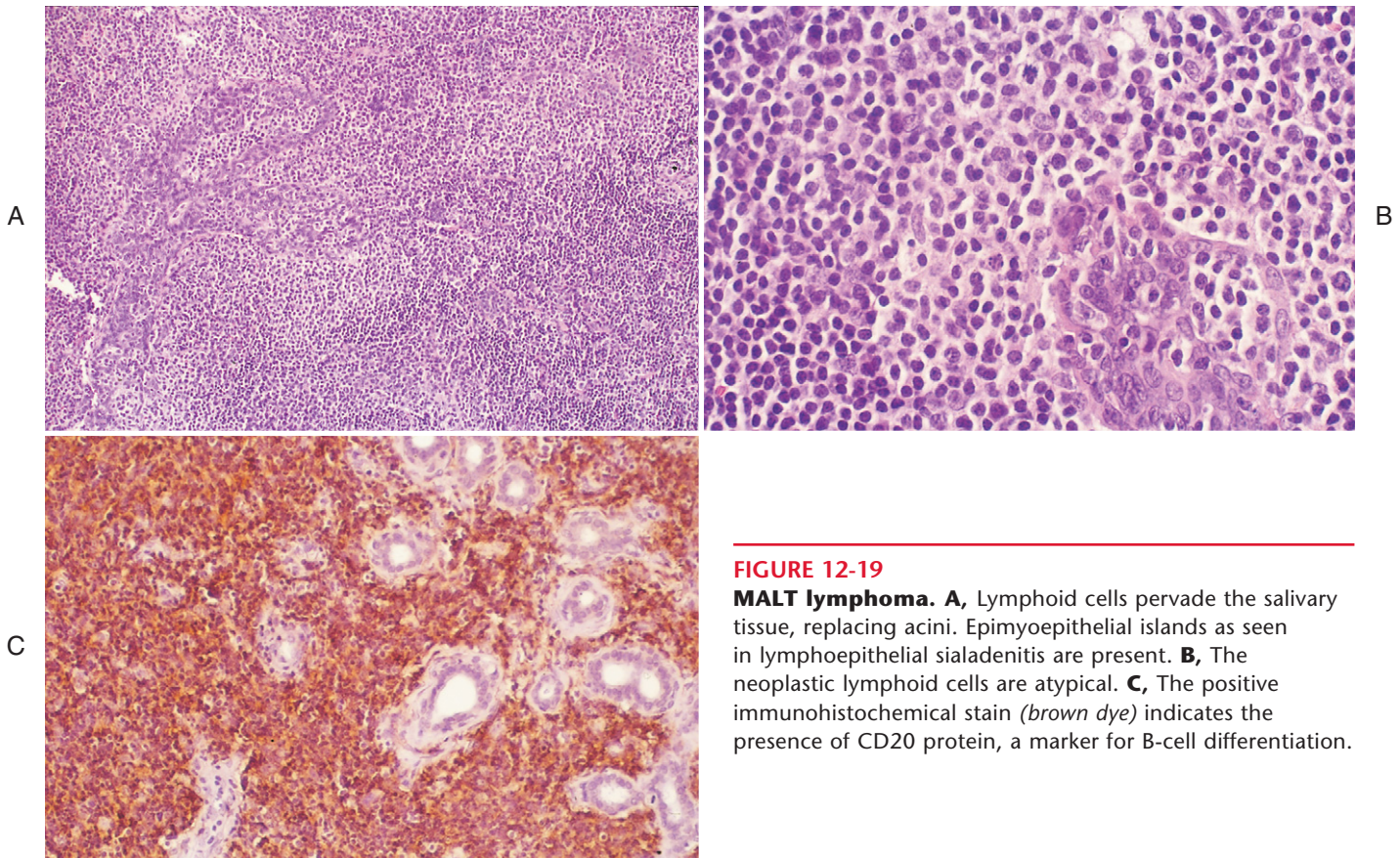


FIGURE 12-19

MALT lymphoma. **A,** Lymphoid cells pervade the salivary tissue, replacing acini. Epimyoepithelial islands as seen in lymphoepithelial sialadenitis are present. **B,** The neoplastic lymphoid cells are atypical. **C,** The positive immunohistochemical stain (brown dye) indicates the presence of CD20 protein, a marker for B-cell differentiation.

Burkitt Lymphoma

BURKITT LYMPHOMA: A form of lymphoma first described in equatorial Africa that is associated with the EBV and has a predilection for the jaws of children.

Burkitt lymphoma, first reported in the equatorial regions of Africa among young children, is associated with EBV. The tumors typically involve extralymphoid sites, showing a predilection for the jaws and viscera, particularly the ovaries. Chromosomal abnormalities are a hallmark of this unique form of lymphoma.

Translocation of a portion of chromosome 8 to chromosomes 2, 14, and 22 is regularly observed. The C-myc oncogene from chromosome 8 is then brought into proximity with the genes encoding immunoglobulin heavy (14), κ light (2), and γ light (22) chain genes. In these circumstances the immunoglobulin gene promoters are believed to cause overexpression of the C-myc oncogene, which is a DNA-binding transcription protein that is active in the process of cell cycling.

CLINICAL FEATURES

Burkitt lymphoma is encountered in three distinct settings: (1) the classic endemic type found in equatorial Africa; (2) a non-African, nonendemic type that has been identified in Europe, the United States, and Asia; and (3) an AIDS-associated type. In African Burkitt lymphoma, children in the first decade of life are affected; however, some cases arise during teenage years. A 2:1 male-to-female ratio is encountered.

Affected children usually have massive tumors of the maxilla or mandible. The tumefactions are firm, and the oral mucosa overlying the masses is often hemorrhagic or ulcerated. Usually the masses are painless and no sensory deficits are noted.

Radiographs disclose massive lesions undergoing osseous resorption, with irregular margins and reactive bone occurring in the molar and premolar regions (Figure 12-20).

Although most tumors are solitary, many can independently involve more than one jaw quadrant. Tooth displacement and root resorption are commonly encountered.

Lymphomatous tissue is also present in the abdomen and may originate within the ovaries. In the nonendemic form, jaw tumors are only seen in 20% of the affected patients.

In AIDS patients, non-Hodgkin lymphoma is the second most prevalent neoplasm, with many of these lesions showing microscopic features in common with Burkitt lymphoma. The lymphomas resembling the Burkitt type tend to arise on the palate and gingiva. The CD4 count is invariably below 200 when the lymphoma first appears. Clinically the lesions appear as soft

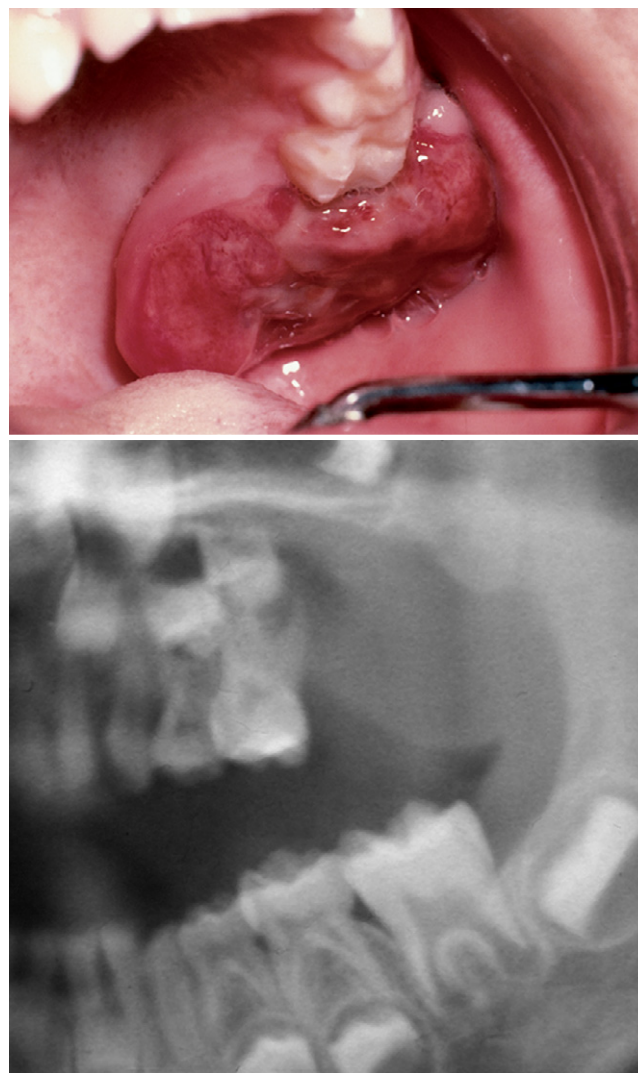


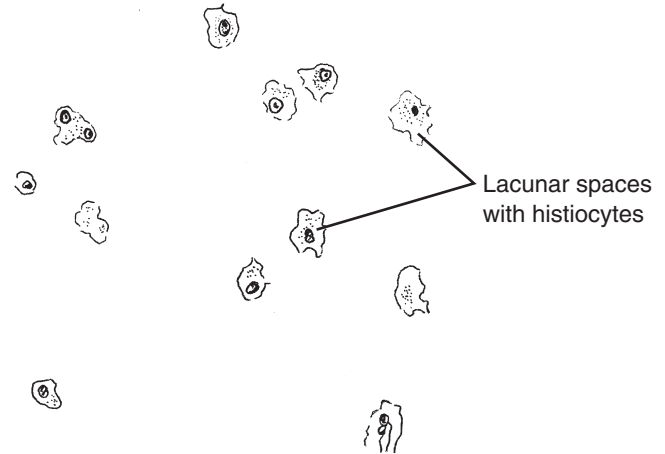
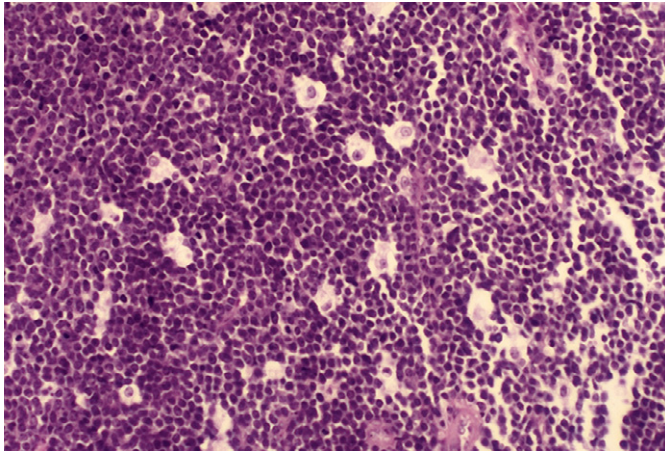
FIGURE 12-20

Burkitt lymphoma. **A**, Massive tumor of posterior maxilla of a young patient. **B**, Radiograph of same patient in **A** exhibiting a large ill-defined radiolucency.

tissue nodular masses and many are hemorrhagic, thus resembling Kaposi sarcoma.

HISTOPATHOLOGY

The basic cell type is a medium, round lymphoblast. A pathognomonic feature of the African form of Burkitt lymphoma is the presence of lacunae that contain macrophages with phagocytized cellular debris. These vacuolated lacunae are rather evenly dispersed among the malignant cell population and under low-power microscopy appear as a starry sky, because the clear lacunae stand out against the dark background of the densely packed lymphocytes (Figure 12-21). The malignant lymphocytes, which comprise the sheetlike proliferation, are

**FIGURE 12-21**

Burkitt lymphoma. Photomicrograph of “starry-sky” appearance that occurs when histiocytes residing within lacunae are scattered throughout diffuse sheets of malignant lymphocytes.

characterized by large, round nuclei with a prominent nuclear membrane, a stippled nucleoplasm, and prominent nucleoli that vary in number from 1 to 4. Each nucleus is surrounded by cytoplasm, which gives the sheets a syncytial appearance. Mitotic activity is often prominent. Tumor cells invade the periodontal ligament and may even extend into the pulps of developing teeth. Similar morphology is seen in the non-African, nonendemic form of Burkitt lymphoma and in HIV.

TREATMENT

Chemotherapy and radiation have been used. Multidrug chemotherapy has dramatic effects on Burkitt lymphoma. Massive tumors may literally melt back to normal jaw dimensions within 2 weeks of initiation. Cyclophosphamide, vincristine sulfate, and methotrexate are commonly prescribed. The 5-year survival rate is less than 30%; although response to chemotherapy is excellent, relapses and the appearance of new lesions tend to occur over time.

Multiple Myeloma

MULTIPLE MYELOMA: A disseminated neoplasm of differentiated B lymphocytes (plasma cells) located within bone.

SOLITARY PLASMACYTOMA: A single tumor of plasma cells often located in the soft tissue of the upper air passages.

Multiple myeloma represents a third type of lymphoma that arises from bone marrow–based B cells, specifically those that have undergone terminal differ-

entiation into plasma cells. As with other lymphomas these tumors are believed to arise from a single cell type and therefore exhibit monoclonality. This clonality can be assessed in tissue sections or by biochemically evaluating the type of immunoglobulin secreted by the neoplastic cells. Multiple myeloma eventually becomes disseminated, involving multiple skeletal sites. This is probably accounted for by biochemical homing mechanisms for terminally differentiated B cells invading other hematopoietic marrow sites.

The solitary plasmacytoma represents a clonal proliferation of plasma cells in an extramedullary site. Some patients have survived for many years with solitary extramedullary plasmacytoma, whereas others have eventually developed disseminated multiple myeloma.

CLINICAL FEATURES

Multiple myeloma affects men and women equally and usually arises during the fourth, fifth, and sixth decades of life. Because the malignant cells occupy the marrow spaces without manifesting any specific signs or symptoms, the disease has often become widely disseminated by the time it is detected. A characteristic feature of multiple myeloma is deep bone pain. Osteolytic lesions are encountered in various bones and are usually quite prominent in the calvarium where they appear as coin-shaped, punched-out radiolucencies. Despite their malignant nature these radiolucent lesions are relatively well defined yet not corticated around their boundaries.

In the jaws the disease may simulate a toothache. Dental radiographs may also show coin-shaped, punched-out radiolucencies or widespread osseous destruction. The radiographic margins are “moth-eaten” without

**FIGURE 12-22**

Multiple myeloma. **A**, Expansion of alveolar bone surrounding a maxillary molar. **B**, Radiograph of lesion depicted in **A** exhibiting a poorly defined radiolucency surrounding the molar.

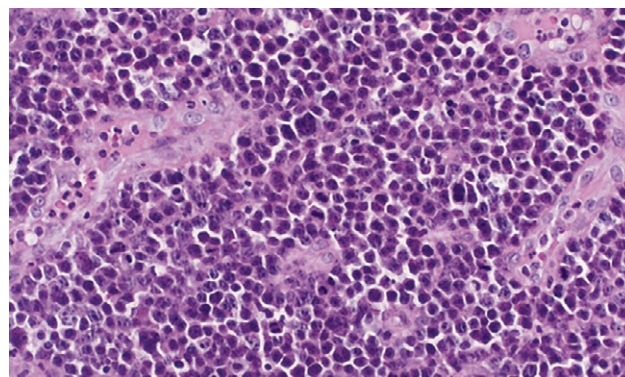
cortication. Teeth within the area of malignancy may become loose (Figure 12-22).

The solitary plasmacytoma occurs as a pendulous mass, usually identified within the nasopharynx. Involvement of the oral mucosa is extremely rare. These plasma cell tumors are usually brought to the patient's attention by such symptoms as nasal speech or nasal stuffiness.

HISTOPATHOLOGY

Multiple myeloma and solitary plasmacytoma show the same microscopic features. Diffuse sheets of plasma cells are encountered with minimal fibrous stroma; instead, small capillary channels course among the plasma cells (Figure 12-23). The individual cells maintain both the nuclear eccentricity encountered in normal plasma cells and the peripheral chromatin beading. Importantly, binucleated forms are common, mitotic figures may be observed, and some degree of nuclear pleomorphism exists.

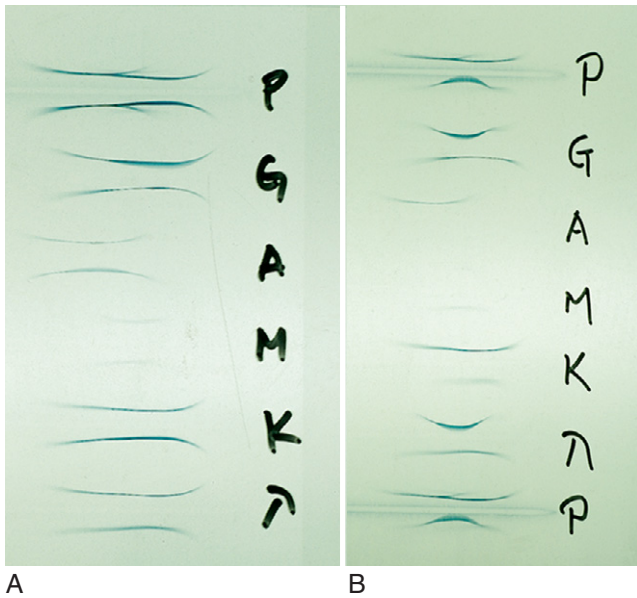
Because plasmacytic infiltrates are quite common in the jaws, particularly in response to odontogenic infections, differentiation from myeloma is sometimes difficult. In most inflammatory conditions that are characterized by high plasma cell populations, other leukocytes are also encountered and the stroma is collagenous. In myeloma the cell population is usually homogeneous. Furthermore, the plasma cells of inflammation are polyclonal and will therefore express both κ and λ immunoglobulin light chains using immunohistochemistry. In multiple myeloma the plasma cell population is

**FIGURE 12-23**

Multiple myeloma. Photomicrograph revealing diffuse sheets of atypical plasma cells with minimal fibrous connective tissue stroma.

monoclonal and will express either κ or λ immunoglobulin light chains but not both.

Multiple myeloma (being a disseminated disease of immunoglobulin-secreting plasma cells) effects a change in serum immunoglobulin levels (Figure 12-24). The total gamma globulins will be increased; on serum immunoelectrophoresis, a monoclonal spike representing a single immunoglobulin class will account for the increased levels. Light chains from immunoglobulins are often excreted into the urine in myeloma and are referred to as *Bence Jones protein*.


FIGURE 12-24

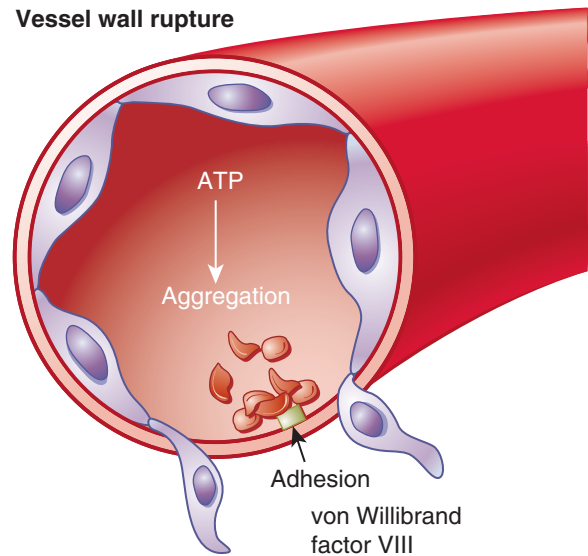
Serum immunoelectrophoresis contrasting a polyclonal hypergammaglobulinemia of inflammation (**A**) with a mono-clonal spike of a multiple myeloma (**B**). P, Total immuno-globulins; G, IgG; A, IgA; M, IgM; K, kappa light chains; and λ , lambda light chains. Under P, the polyclonal increase in **A** is characterized by a broad curve, indicating a variety of immunoglobulin classes; whereas in **B** the monoclonal spike is small, indicating a single immunoglobulin class that is IgG with lambda clonality.

TREATMENT

Multiple myeloma carries a poor prognosis despite intensive chemotherapy. Multidrug regimens are used to arrest cell division in an attempt to eliminate the disease. Total body irradiation with bone marrow transplantation is another treatment option.

BLEEDING DISORDERS

Hemostasis is achieved by cooperative functions between blood thrombocytes and coagulation factors. During the primary stage of hemostasis, once a vessel wall is violated, platelet adhesion ensues. This adhesion phenomenon requires the presence of the von Willebrand factor and other specific adhesion proteins on the thrombocyte plasma membrane. Platelet adhesion to the subintimal connective tissue then triggers biochemical changes within the thrombocytes with the release of proteins that facilitate aggregation between one platelet and its neighbor. These aggregated platelets then form the initial plug, which prevents bleeding (Figure 12-25). It is therefore axiomatic that individuals who have a deficiency in platelet numbers and individuals who have functional disturbances in platelet adhesion will suffer from bleeding episodes. In general, most platelet dis-


FIGURE 12-25

Thrombocyte function. When a vessel wall is damaged, platelets will adhere to the subintimal connective tissue aided by von Willebrand Factor VIII adhesion protein. Platelets aggregate with one another by virtue of other adhesion molecules, activated by adenosine triphosphate (ATP) conversion to cyclic adenosine monophosphate (AMP).

BOX 12-2

Hemorrhagic Diathesis and Purpura

PLATELET DISORDERS

Autoimmunity
Chemotherapy
Defective adhesion
Defective aggregation
Genetic
Irradiation
Leukemia
Prostaglandin inhibitors

COAGULATION FACTOR DEFICIENCY

Genetic
Primary liver disease
Biliary obstruction
Steatorrhea
Anticoagulant drugs

VASCULAR WALL FRAGILITY

Scurvy
Genetic

orders are characterized by cutaneous and mucosal petechiae. The initial platelet plug is not stable but becomes a more adequate seal after the formation of a fibrin clot. Box 12-2 lists many of the causes of bleeding disorders (hemorrhagic diathesis) and easy bruising (purpura) encountered in patients.

PLATELET DISORDERS

Thrombocytopenia

THROMBOCYTOPENIA: A decrease in the number of circulating blood platelets that can be caused by a variety of factors.

Total circulating blood platelets are normally between 250,000 and 400,000/mm³ of blood. A decrease in number may occur because of a maturation arrest, a myelophthistic response in the marrow, or autoimmune events after release into the circulation. Importantly, when the platelet count drops below 35,000 cells/mm³, severe catastrophic bleeding may occur subsequent to trauma or surgery. The most common underlying causes that result in thrombocytopenia include administration of cytotoxic chemotherapeutic drugs, leukemia, and autoimmune thrombocytopenic purpura, in which antiplatelet antibodies are observed. The autoimmune form occurs in HIV-infected patients as well and is referred to as *idiopathic thrombocytopenic purpura* (ITP). The cause for the generation of antiplatelet antibodies is unknown.

CLINICAL FEATURES

Petechial hemorrhages are the most common form of purpura encountered in thrombocytopenia and are characterized by pinpoint red or brown macules of the skin. They may occur on any surface within the oral cavity but are more frequently seen on the palate (Figure 12-26). In the differential diagnosis, however, it should be noted that palatal petechiae are more often caused by suction. Clicking the palate against the tongue is common when an individual suffers from an upper respiratory infection and has an itchy throat. Palatal petechiae are also reported to occur from fellatio. Oral petechiae secondary to thrombocytopenia are usually accompanied by cutaneous petechiae as well. Additionally, patients may complain of spontaneous gingival hemorrhage.

LABORATORY FINDINGS

Thrombocytopenia is diagnosed by obtaining a platelet count. When leukemia is suspected, a complete blood count should be obtained because leukemia is frequently associated with a drop in the platelet count. The bleeding time is a clinical assessment of platelet numbers and adherence. The clinician performs the test by placing a blood pressure cuff on the patient's arm and applying a pressure of 40 mm mercury. Below the cuff the forearm is penetrated with a 1 mm blood lancet. The small focus of hemorrhage is dabbed every 15 seconds with a piece of filter paper; when blood can no longer be identified on the paper, the bleeding time has been reached. In patients with normal functioning and adequate numbers of platelets, the bleeding time usually varies between 5 and 7 minutes.



FIGURE 12-26

Palatal petechiae. Multiple small foci of superficial vessel bleeding occurs because of the fragility of the vessel wall or altered clotting factors when minor trauma to the area is encountered.

TREATMENT

Before treatment can be planned, the underlying cause of a reduction in platelets must be determined. A platelet count below 35,000 can lead to a life-threatening hemorrhage after oral surgery. If surgery must be performed or if it is essential that an infected tooth be extracted, the patient will need to be hospitalized and platelet infusions must be administered.

Thrombasthenia

THROMBASTHENIA: A functional group of diseases characterized by defective adherence or aggregation of platelets.

Although a hemorrhagic diathesis will occur when the number of platelets drops below critical levels, functional impairment can also result in purpura. Defects in platelet adhesion or aggregation culminate in inadequate plugging of ruptured vessels, and the disease is referred to as *thrombasthenia*. Aspirin toxicity with its effects on prostaglandin synthesis is one of the more clinically common defects in platelet adhesion and aggregation. In addition, heritable diseases exist in which patients fail to synthesize functionally intact adhesion molecules on the platelet surface. One such disorder that also affects the coagulation pathway is von Willebrand

disease, in which an important adhesion molecule is defective. In addition, Factor VIII of the intrinsic pathway is also defective. Various subtypes of von Willebrand disease have been uncovered.

CLINICAL FEATURES

In salicylate toxicity, as in von Willebrand disease and other rare forms of thrombasthenia, petechial hemorrhages are the hallmark. Therefore the clinical features simulate those seen in thrombocytopenia. Similarly, when petechiae occur within the oral cavity, the skin is also affected.

LABORATORY FINDINGS

The platelet count in thrombasthenia is normal. Although a functional assay for platelet aggregation can be performed in the clinical laboratory, the bleeding time is prolonged. In addition, assays are available to access levels of von Willebrand Factor VIII.

TREATMENT

Platelets that have become defective because of salicylate toxicity are impaired for the life of the platelet. Because new thrombocytes are constantly being synthesized, the defect is usually reversed within 1 week after withdrawal of aspirin. Dipyridamole is a platelet adhesion inhibitor prescribed to prevent thromboembolic disease. Prolonged bleeding can be a problem, and medical consultation should be sought before performing oral surgery. Currently the heritable forms cannot be adequately treated; however, should a hemorrhagic crisis occur, platelet infusions will be necessary. Von Willebrand disease is usually mild despite the fact that platelet adhesion and coagulation Factor VIII are defective. It is not uncommon for a diagnosis of von Willebrand disease to be made after prolonged bleeding subsequent to dental extraction, even in adult years.

CAPILLARY FRAGILITY

The fibrous coat or adventitia of small-caliber vessels is defective or inadequate in ascorbic acid deficiency and in the heritable disease, hereditary hemorrhagic telangiectasia. Vitamin C is an important cofactor in collagen fibrillogenesis. When dietary intake is inadequate, collagen synthesis is impaired; this is usually manifested in vessel walls. In hereditary hemorrhagic telangiectasia, a structural deformity is found involving the integrity of the small vessel vascular wall.

Vitamin C Deficiency (Scurvy)

VITAMIN C DEFICIENCY (SCURVY): A systemic disease caused by lack of vitamin C dietary intake in which vascular wall integrity and wound repair mechanisms are defective.

Vitamin C deficiency (scurvy) is rarely seen in the industrialized world, because most individuals have sufficient vitamin C in their diets. Citrus fruits and tomatoes are the primary sources of this vitamin. Therefore scurvy is usually encountered in third world countries, where adequate nutritional intake is not available.

CLINICAL FEATURES

Purpura is one of the main manifestations of scurvy and occurs because of vascular wall fragility. The purpuric lesions may occur in the oral mucosa and on the skin and are represented by petechia and ecchymosis. Although the bruising usually occurs after traumatic provocation, in severe scurvy, spontaneous purpura may be identified.

Because the collagen fibers of the periodontal ligaments may also be defective, severe periodontal disease may be encountered and spontaneous tooth loss will occur.

Scorbutic changes may also evolve in bone matrices, leading to pathologic fractures.

Because vitamin C is important during healing, ulcerations or lacerations may persist and become secondarily infected. These ulcerations can involve the oral mucosa.

HISTOPATHOLOGY

Microscopically, vascular wall changes are not discernible in scurvy; although pathologic changes are identifiable with electron microscopy. Skin or mucosal biopsies show extravasation of erythrocytes, extravascular clot formation within tissue, and hemosiderin pigment deposition. The disease is diagnosed by assessing the patient's history, clinical findings, and serum ascorbic acid levels.

TREATMENT

Scurvy is reversed by adequate dietary intake of ascorbic acid. The vascular changes are reversible. Periodontal tissue breakdown, however, is permanent; lost alveolar bone will not regenerate after adequate vitamin intake.

Hereditary Hemorrhagic Telangiectasia

HEREDITARY HEMORRHAGIC TELANGIECTASIA:

An inherited disease in which vascular walls are defective and multiple vascular dilatations occur in the mucous membranes of the upper aerodigestive tract.

Inherited as an autosomal dominant trait, hereditary hemorrhagic telangiectasia (**Rendu-Osler-Weber syndrome**) affects the integrity of vascular walls. Lesions are most prominent in the head and neck areas, invariably involving the oral mucosa. The damaged vessels are dilated, creating multiple reddish-purple papules that are separated from one another by normal-appearing skin



FIGURE 12-27
Hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome). Multiple small raised reddish papules are present on the dorsum of the tongue. The patient also exhibited similar lesions on other mucosal surfaces and the skin.

or mucosa. They typically occur on the dorsum of the tongue (Figure 12-27), on the lips, and in the nasal mucosa. The affected vessels are larger than capillaries, and trauma may cause prolonged hemorrhaging. Epistaxis is common. The bleeding is usually stopped by direct compression.

HISTOPATHOLOGY

In hereditary hemorrhagic telangiectasia, dilated vascular channels engorged with erythrocytes are seen and erythrocyte extravasation is common, with the deposition of hemosiderin pigment in the perivascular connective tissue. The vessel wall defect is not apparent with light microscopy; instead, electron microscopy is needed to demonstrate the vascular abnormality. No altered laboratory values exist regarding platelet numbers or aggregation in this disease. Clotting factors are normal.

TREATMENT

No treatment exists for this condition, because it represents a structural defect. Hemorrhage can sometimes be problematic, and cases of severe epistaxis can occur. Compression with gauze or cotton packs will usually result in cessation of hemorrhage, and the affected vessel may be cauterized. For cosmetic reasons, particularly around the lip area, the cutaneous papules can be treated by laser therapy.

COAGULATION DISORDERS

The coagulopathies are diseases caused by defective proteins that are components of the coagulation cascade (Figure 12-28). They may be *hereditary*, the result of mu-

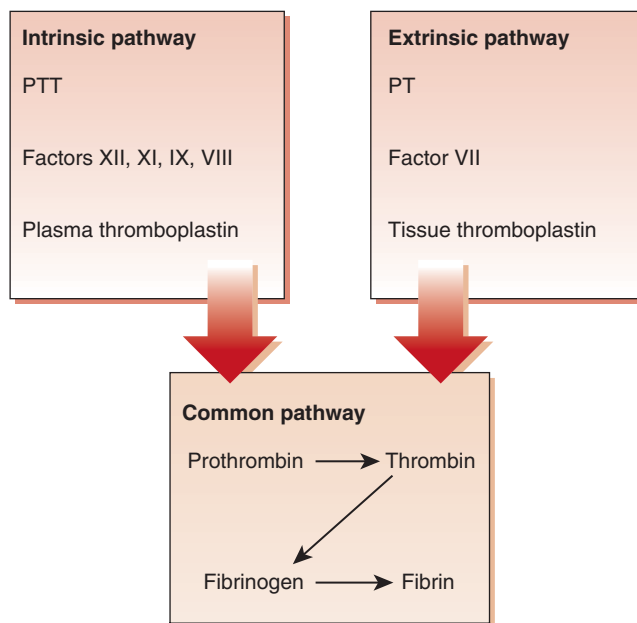
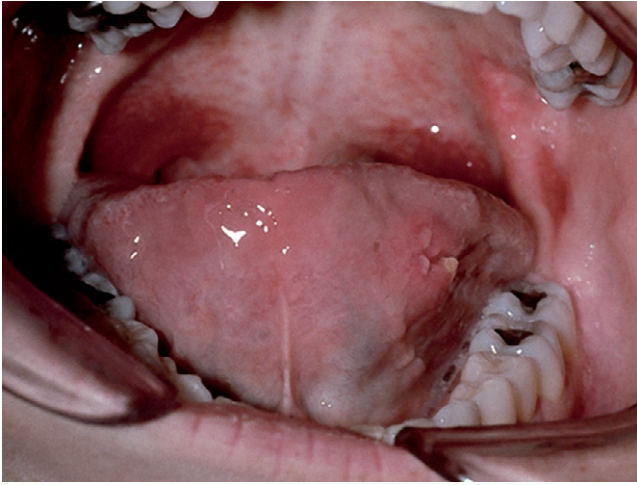


FIGURE 12-28
Clotting factor pathways. The extent that the intrinsic pathway is able to function is assessed by the partial prothrombin time (PTT), whereas that of the extrinsic pathway is evaluated by a determination of the prothrombin time (PT). Both pathways converge into a common pathway, culminating in the formation of a fibrin clot.

tations in the genes that encode a specific coagulation factor, or *acquired*, involving multiple coagulation factors. Most of the hereditary coagulopathies are quite rare, with the exception of hemophilia A. Acquired coagulation disorders occur primarily as a consequence of chronic liver disease and among patients taking antithrombotic medications such as Coumadin and Persantine. Because the majority of coagulation factors are synthesized within the liver, any disease that leads to the death of hepatocytes will result in a coagulopathic disorder. Therefore hepatitis, alcoholic cirrhosis, biliary atresia, and biliary cirrhosis can all be associated with prolonged bleeding times. Malabsorption syndromes, particularly steatorrhea, involve defects in fat absorption. Inadequate absorption of fat results in a reduction of the fat-soluble vitamin K, an essential factor for the synthesis of five clotting factors. The inability to absorb vitamin K predisposes to coagulopathies and a bleeding tendency.

Hemophilia

HEMOPHILIA: A group of bleeding diseases that evolve as a result of hereditary defects in the production of proteins necessary for normal blood coagulation.

**FIGURE 12-29**

Ecchymosis. The areas of bilateral superficial interstitial bleeding of the posterior soft palate (arrows) present in this patient are commonly encountered after minor trauma in patients with hereditary or acquired coagulopathies.

The two major forms of hemophilia (A and B) are hereditary. The defective proteins are components of the intrinsic pathway of clotting that functions within blood vessels. Alternatively, the extrinsic pathway is activated extravascularly and is important in soft tissue clot formation and wound repair. Although a different group of clotting factors is required for the extrinsic pathway, the intrinsic and the extrinsic pathways culminate in the formation of thromboplastins. The two pathways then share a common route for the final synthesis of the fibrin protein network, the essence of normal clot formation. Genetic defects of various other clotting factors are extremely rare.

CLINICAL FEATURES

Purpura is the clinical sign common to all types of coagulopathies. The purpuric lesions are characterized by diffuse purple, red, or brown macules commonly referred to as *bruises* or *ecchymosis* (Figure 12-29). These ecchymotic changes may be seen on the facial skin and the oral mucosa, typically occurring after minor trauma. Hemarthrosis (bleeding within the joints) is another common finding in coagulation disorders, being more prevalent in individuals with hereditary factor deficiency.

Hemophilia A, a hereditary deficiency of Factor VIII, and *hemophilia B*, a hereditary deficiency of Factor IX, are the most common of the genetic factor deficiencies. Hemophilia A is approximately 10 times as prevalent as hemophilia B.

Afibrinogenemia, a hereditary deficiency of Factor I, is even less commonly seen; deficiencies in the other specific factors are extremely rare. In all heritable coag-

ulation disorders the disease becomes apparent in early childhood, often after the child engages in some physical activity that results in profound bruising or hemarthrosis. In addition, the eruption of deciduous teeth may trigger spontaneous gingival hemorrhage. Dental extraction or oral surgical procedures are contraindicated without taking appropriate precautions, which often necessitate hospitalization.

Acquired coagulopathy is commonly associated with liver cirrhosis and may be accompanied by a variety of other signs and symptoms, depending on the severity of the liver parenchymal damage. The acquired coagulopathies encountered in liver disease and anticoagulant therapy share clinical features with those encountered in the two major forms of hemophilia (A and B) and afibrinogenemia.

In addition to coagulation factors, the liver synthesizes a variety of other proteins, including albumin. Albumin is the major protein component of blood and is largely responsible for maintaining the positive osmotic pressure in the vascular compartment. As albumin levels decrease and the total serum protein levels drop, intravascular osmotic pressure decreases, leading to loss of fluid from the vascular compartment to the surrounding tissues with resultant edema and ascites. Because estrogens are metabolized in the liver thereby preventing their buildup in the blood, parenchymal necrosis of liver tissue will lead to increased estrogen levels that may predispose to breast enlargement (gynecomastia) in males. The conjugation of bilirubin by hepatocytes may also be impaired, leading to hyperbilirubinemia and jaundice. Finally, chronic liver failure with sclerosis induces a stasis in blood flow through the portal system with attending portal hypertension. This stasis culminates in the dilatation of veins that drain into the portal system, including the esophageal, hemorrhoidal, and umbilical veins. Esophageal varices, hemorrhoids, and abdominal caput medusae are signs of advanced liver disease and are attended by severe coagulation defects with ecchymosis.

Perhaps the most common cause of coagulopathy is anticoagulant therapy. Coumadin, most commonly prescribed, interferes with the formation of many coagulation factors by inhibiting vitamin K, a coenzyme necessary for their synthesis. Patients properly placed on anticoagulant therapy receive doses at levels that prevent spontaneous profound thrombosis yet do not place the patient in jeopardy of severe hemorrhaging. Nevertheless, the drug level cannot always be precisely monitored; some of these patients will develop ecchymosis.

HISTOPATHOLOGY

Unlike platelet disorders in which petechial hemorrhages occur, coagulopathies are associated with more severe venous hemorrhage; therefore the purpura is often large

and more diffuse. Microscopically, diffuse zones of extravasated erythrocytes and deposits of hemosiderin pigment are present in the surrounding connective tissue. The clinician is in the best position to make the diagnosis by conducting assays that measure the intrinsic and extrinsic pathways of coagulation. The prothrombin time (PT) now standardized as the international normalized ratio (INR) examines the extrinsic pathway, whereas the partial thromboplastin time (PTT) assesses the intrinsic pathway. Patients taking Coumadin or those with liver disease are usually monitored by the PT, whereas the PTT will be prolonged in hemophilia A and B.

TREATMENT

Oral surgical procedures in patients with a hemorrhagic diathesis can be life threatening if appropriate precautions are not observed. In general, a PT or PTT that is prolonged more than three times the laboratory control levels is an indication that oral or periodontal surgery should not be undertaken without precautions. If tooth extraction is required, the patient must be hospitalized and coagulation factor supplementation must be available.

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Glossary

ABRASION: An abnormal loss of tooth structure because of nonmasticatory physical friction.

ACANTHOSIS: Excessive thickening of the spinous layer of squamous epithelium, resulting in broadening and elongation of the rete pegs.

ACINIC CELL CARCINOMA: A malignant salivary gland tumor primarily of the parotid gland and composed of pale-staining acini cells usually in a solid or follicular pattern with little visible stroma.

ACRAL LENTIGINOUS MELANOMA: Brown, irregularly shaped, macular lesion of the skin of the palms of the hands and soles of the feet that undergoes progression to nodular melanoma.

ACUTE LYMPHONODULAR PHARYNGITIS: A localized infection of coxsackievirus A (subtype 10) consisting of yellow or white papules surrounded by an erythematous zone confined to the lymphoid tissues of the posterior soft palate and nasopharynx that lasts from 1 to 2 weeks.

ACUTE OSTEOMYELITIS: A rapidly destructive inflammatory process within bone that consists of granulation tissue, purulent exudate, and islands of nonvital bone (sequestra).

ACUTE PRIMARY HERPETIC GINGIVOSTOMATITIS: An uncommon clinical presentation of an initial herpes simplex infection in which multiple shallow ulcers are present throughout both the keratinized and gland-bearing intra-oral surfaces; accompanied by systemic symptoms of fever, lymphadenopathy, and myalgia.

ACUTE PSEUDOMEMBRANEOUS CANDIDIASIS: A clinical form of *Candida albicans* infection that consists of creamy, loose patches of desquamative epithelium containing numerous matted mycelia over an erythematous mucosa that is easily removed; it is common in patients with more severe predisposing factors.

ADENOID CYSTIC CARCINOMA: A malignant salivary gland tumor composed of cuboidal cells in a solid, cribriform ("Swiss cheese") or tubular pattern with a predilection for invading perineural lymphatic spaces.

ADENOID SQUAMOUS CELL CARCINOMA: An uncommon type of low-grade epithelial malignancy of the sun-exposed skin of the face and lower lip.

ADENOMATOID ODONTOGENIC TUMOR: A well-circumscribed lesion derived from odontogenic epithelium that usually occurs around the crowns of unerupted anterior teeth of young patients and consists of epithelium in swirls and ductal patterns interspersed with spherical calcifications.

ADENOSQUAMOUS CARCINOMA: Rare, aggressive carcinoma of the mucosa consisting of a mixture of malignant squamous and glandular cells.

AGRANULOCYTOSIS: A marked decrease in circulating granulocytes, particularly neutrophils, attributable to a variety of causes.

AMELOBLASTIC CARCINOMA: An aggressive neoplasm of the mandible or maxilla in which the epithelial component exhibit features of ameloblastoma but with notable cytologic malignancy.

AMELOBLASTIC FIBROMA: A circumscribed lesion predominantly located over unerupted molars in young patients; the epithelium and connective tissue recapitulate the cap and bell stages of odontogenesis.

AMELOBLASTIC FIBRO-ODONTOMA: An expansile growth in young patients that contains the soft tissue components of ameloblastic fibroma and the hard tissue components of complex odontoma.

AMELOBLASTOMA: A locally aggressive neoplasm of odontogenic epithelium that has a wide spectrum of histologic patterns resembling early odontogenesis.

AMELOGENESIS IMPERFECTA: A heterogeneous group of genetic disorders exhibiting faulty enamel formation.

ANEURYSMAL BONE CYST: An uncommon lesion located primarily in the posterior mandible and maxilla with clinical features similar to central giant cell lesion; it contains many large blood-filled spaces separated by connective tissue septa containing giant cell tissue.

ANGIOEDEMA: A recurring rapid swelling of the lips and adjacent structures in susceptible patients that occurs after contact with an allergen, antiinflammatory medication, or exposure to the elements.

ANGIOSARCOMA: A malignant, rare, rapidly growing lesion of endothelial cells that is more common in young patients and has a poor prognosis.

ANGULAR CHEILITIS (PERLÈCHE): Symptomatic bilateral fissures of the corners of the mouth that are common in patients with *Candida albicans* infection in other parts of the mouth and often intensified with mouth overclosure; it requires treatment with antifungal medication.

ANKYLOGLOSSIA: Lack of normal tongue mobility caused by the presence of an abnormal fibrous tissue attachment between its ventral surface and the floor of the mouth.

ANKYLOSIS: Fusion of the cementum or dentin to the surrounding alveolar bone after loss of the intervening periodontal membrane.

APHTHOUS MAJOR: One or two uncommon, large, superficial, painful ulcers usually present on the labial mucosa and soft palate.

APHTHOUS MINOR: Commonly encountered, painful, small, superficial ulcers of the oral gland-bearing mucosa occurring episodically in clusters of one to five lesions.

ASPERGILLOSIS: An infection commonly located in the lungs of immunocompromised patients and occasionally occurring as a destructive lesion of the maxillary sinuses, anterior palate, and nasal passages as the result of inhalation of spores of *Aspergillus fumigatus* and *A. flavus*; it is best treated in the oral area with surgical debridement followed by amphotericin B and azole fungicides and with management of the predisposing condition.

ATROPHIC (ERYTHEMATOUS) CANDIDIASIS: A clinical form of *Candida albicans* infection in which the mucosa is thinned, smooth, and bright red with symptoms of burning and increased sensitivity; it is commonly found on the palate under a denture but also on the tongue and other mucosal surfaces.

ATTRITION: Loss of tooth structure because of the mechanical action of mastication.

AVULSION: The forceful displacement of a tooth in its socket.

BACTERIA-ASSOCIATED LEUKOCYTOSIS: A marked elevation in levels of circulating neutrophils occurring as a result of an infection by pyogenic bacteria.

BASAL CELL CARCINOMA: Common, locally destructive, nonmetastasizing malignancy of the skin; composed of medullary patterns of basaloid cells.

BASALOID SQUAMOUS CELL CARCINOMA: Rare, aggressive form of poorly differentiated squamous cell carcinoma consisting of medullary patterns of cells with central areas of necrosis.

BEHÇET SYNDROME: A multisystem disease of uncertain pathogenesis consisting of multiple oral, anogenital, and ocular aphthouslike lesions; frequently with arthralgia and associated central nervous system involvement.

BENIGN FIBRO-OSSEOUS LESIONS: A collection of non-neoplastic intraosseous lesions that replace normal bone and consist of a cellular fibrous connective tissue within which nonfunctional osseous structures form.

BENIGN FIBROUS HISTIOCYTOMA: A benign neoplasm of fibroblasts with a propensity to differentiate into histiocytes.

BENIGN MIGRATORY GLOSSITIS: Multiple, sensitive, irregularly shaped erythematous patches of the tongue with arcuate white rims that enlarge and change shape daily.

BENIGN SOLITARY FIBROUS TUMOR: A benign neoplasm of fibroblastic cells with production of collagen that is hypercellular and typically labels with the CD 34 histochemical marker.

BIOPSY: The removal of a sample of living tissue for laboratory examination.

BURKITT LYMPHOMA: A form of lymphoma first described in equatorial Africa that is associated with the Epstein-Barr virus (EBV) and has a predilection for the jaws of children.

CALCIFYING EPITHELIAL ODONTOGENIC TUMOR: A locally aggressive tumor consisting of strands and medullary patterns of squamous and clear cells that are often accompanied by spherical calcifications and amyloid-staining hyaline deposits.

CALCIFYING ODONTOGENIC CYST: A rare, well-circumscribed, solid or cystic lesion derived from odontogenic epithelium that microscopically resembles ameloblas-

toma but differs by containing ghost cells and spherical calcifications.

CARCINOMA IN SITU: The most severe stage of epithelial dysplasia, involving the entire thickness of the epithelium, with the epithelial basement membrane remaining intact.

CELLULITIS: A painful swelling of the soft tissue of the mouth and face resulting from a diffuse spreading of purulent exudate along the fascial planes that separate the muscle bundles.

CEMENTOBLASTOMA: A benign, well-circumscribed neoplasm of cementum-like tissue growing in continuity with the apical cemental layer of a molar or premolar that produces expansion of cortical plates and pain.

CEMENTO-OSSEOUS LESIONS: Benign fibro-osseous lesions of the jaws closely associated with the apices of teeth and containing amorphous spherical calcifications thought to resemble an aberrant form of cementum; lesions are usually without signs or symptoms.

CEMENTO-OSSIFYING FIBROMA: A well-demarcated, encapsulated, expansile intraosseous lesion of the jaws composed of cellular fibrous tissue containing spherical calcifications and irregular, randomly oriented bony structures.

CENTRAL GIANT CELL LESION: An intraosseous destructive lesion of the anterior mandible and maxilla in which larger lesions expand the cortical plates, cause movement of teeth, and produce root resorption; it is composed of multinucleated giant cells in a background of mononuclear fibrohistiocytic cells and red blood cells.

CERVICAL LYMPHOEPITHELIAL CYST: An unusually large lymphoepithelial cyst located on the lateral aspect of the neck.

CHEILITIS GLANDULARIS: Enlargement of the lower lip because of chronic inflammation of the minor salivary glands and distention of excretory ductal structures.

CHERUBISM: An autosomal dominant fibro-osseous lesion of the jaws involving more than one quadrant that stabilizes after the growth period, usually leaving some facial deformity and malocclusion.

CHONDROSARCOMA: Uncommon malignant bone neoplasm in the jaws, usually of the anterior maxilla, consisting of a proliferation of plump chondroblasts or spindle-shaped mesenchymal cells and abnormal cartilage but no osteoid or bone.

CHRONIC GRANULOMATOUS DISEASE OF CHILDHOOD: An inherited disorder of neutrophil and monocyte function that predisposes patients to opportunistic infections.

CHRONIC HYPERPLASTIC CANDIDIASIS: A clinical form of *Candida albicans* infection consisting of white plaques or papules against an erythematous background containing hyphae in the parakeratin layer of the thickened epithelium.

CHRONIC SCLEROSING SIALADENITIS: Chronic inflammation of salivary gland tissue resulting in replacement of acini by lymphocytes, plasma cells, and fibrous tissue but sparing much of the ductal architecture.

CLEFT LIP: A developmental defect, usually of the upper lip, characterized by a wedge-shaped defect resulting from the failure of two parts of the lip to fuse into a single structure.

CLEFT PALATE: A developmental defect of the palate characterized by a lack of complete fusion of the two lateral portions of the palate, resulting in a communication between the oral cavity and the nasal cavity.

COCCIDIOIDOMYCOSIS: A chronic lung infection as the result of inhalation of spores of *Coccidioides immitis* common in the San Joaquin Valley of California that may have associated chronic ulcers in the mouth resembling a malignancy; it is best treated with amphotericin B.

CONCRESCENCE: Union of the roots of two or more normal teeth caused by confluence of their cementum.

CONDYLOMA ACUMINATUM: Multiple papillary or sessile focal areas of epithelial hyperplasia of the genital and oral mucosa that contain koilocytes and human papilloma virus 6 or 11 (HPV-6 or HPV-11) and are difficult to eradicate.

CONGENITAL GINGIVAL GRANULAR CELL TUMOR: A pedunculated growth on the anterior maxilla or mandible of newborns that is composed of granular cells.

CRYPTOCOCCOSIS: A chronic infection of the lungs as the result of the inhalation of spores of *Cryptococcus neoformans* carried in bird droppings, with a predilection for spread to the central nervous system; oral chronic ulcers primarily occur in immunocompromised patients and are best treated with amphotericin B.

CYCLIC NEUTROPENIA: An idiopathic disease in which episodic defects in neutrophil maturation in the bone marrow result in periodic decreases in circulating neutrophils.

CYST: A pathologic cavity, lined by epithelium, containing fluid or semisolid material.

DENS EVAGINATUS: A developmental anomaly characterized by a cusplike supernumerary focal enamel protrusion on the occlusal or lingual surface of the crown.

DENS INVAGINATUS: A developmental dental anomaly characterized by a deep enamel-lined pit that extends for varying depths into the underlying dentin, often displacing the pulp chamber and sometimes altering (expanding) the shape of the root.

DENTAL LAMINA CYST OF THE NEWBORN: Small, sometimes multiple, raised cystic nodules that occur on the alveolar ridges of infants; they are derived from rests of the dental lamina and consist of a keratin-filled cystic cavity.

DENTIGEROUS CYST: An odontogenic cyst that surrounds the crown of an impacted tooth; it is caused by fluid accumulation between the reduced enamel epithelium and the enamel surface, resulting in a cyst in which the crown is located within the lumen and root or roots outside.

DENTIN DYSPLASIA: A hereditary defect in dentin formation in which the coronal dentin and tooth color are normal; the root dentin is abnormal with a gnarled pattern and associated shortened and tapered roots.

DENTINOGENESIS IMPERFECTA: A hereditary defect consisting of opalescent teeth composed of irregularly formed and undermineralized dentin that obliterates the pulp chambers and pulp canals.

DERMOID CYST: A cyst of the midline of the upper neck or the anterior floor of the mouth of young patients, derived from remnants of embryonic skin, consisting of a lumen lined by a keratinizing stratified squamous epithelium and containing one or more skin appendages such as hair, sweat, or sebaceous glands.

DESMOPLASTIC FIBROMA: A benign diffuse infiltrative proliferation of fibroblasts or myofibroblasts and mature collagen occurring primarily within the mandible in young patients.

DILACERATION: A sharp bend or angulation involving the root of a tooth.

DRUG-INDUCED GINGIVAL HYPERPLASIA: A generalized increase in the fibrous component of the gingiva in patients who have been taking long-term doses of phenytoin, cyclosporine, and nifedipine.

EPIDERMOID CYST: A cyst of skin with a lumen lined by keratinizing stratified squamous epithelium, usually filled with keratin and without skin appendages in the capsule wall.

EPIDERMOLYSIS BULLOSA: A generalized desquamating condition of the skin and mucosa with associated scarring, contractures, and dental defects that occur in three main hereditary forms in children and one acquired form in adults.

EPITHELIAL ATROPHY: A reduction in the normal thickness of epithelium that involves less than the entire thickness of the epithelium.

EPITHELIAL DYSPLASIA: A premalignant change in epithelium characterized by a combination of cellular and architectural alterations that involve less than the entire thickness of the epithelium.

EROSION: A loss of tooth structure as the result of nonbacterial chemical causes.

ERUPTION CYST: An odontogenic cyst with the histologic features of a dentigerous cyst that surrounds a tooth's crown that has erupted through bone but not soft tissue and is clinically visible as a soft fluctuant mass on the alveolar ridges.

ERUPTION SEQUESTRUM: A small spicule of calcified tissue that is extruded through the alveolar mucosa that overlies an erupting molar.

ERYTHEMA MULTIFORME: A widespread hypersensitivity reaction that occurs in mild and severe forms and has tissue reactions centered on the superficial vessels of the skin and mucous membranes; it usually occurs in patients as the result of an inciting agent.

ERYTHROPLAKIA: A clinical term for a red patch of the oral mucosa, frequently caused by epithelial dysplasia, carcinoma in situ, or squamous cell carcinoma.

EWING SARCOMA: Rare malignant bone neoplasm of uncertain cell origin in young patients; the lesion is composed of anaplastic small, dark, round cells containing glycogen granules and intermediate filaments.

EXOSTOSIS: An exophytic nodular growth of dense cortical bone commonly located on maxillary or mandibular buccal alveolar bone, usually in the bicuspid and molar area.

EXTERNAL RESORPTION: A loss of tooth structure that begins on the outer surface and extends inward toward the pulp.

FETAL ERYTHROBLASTOSIS: A form of hemolytic anemia that occurs in utero when maternal antibodies develop against antigens on fetal red blood cells not present in the mother and intermingle with fetal blood.

FIBROMATOSIS: A benign diffuse infiltrative proliferation of fibroblasts and mature collagen occurring within the soft tissues of the head and neck in young patients.

FIBROSARCOMA: A malignant neoplasm of fibroblastic cells.

FIBROUS DYSPLASIA: An asymptomatic regional alteration of bone in which the normal architecture is replaced by fibrous tissue and nonfunctional trabeculae-like osseous structures; lesions may be monostotic or polyostotic, with or without associated endocrine disturbances.

FISSURED TONGUE: Multiple, deep, linear creases on a usually atrophic dorsal tongue of older patients that is associated with multiple local and systemic conditions that may become symptomatic when secondarily infected.

FISTULA: A drainage pathway or abnormal communication between two epithelium-lined surfaces because of destruction of the intervening tissue.

FLORID CEMENTO-OSSEOUS DYSPLASIA: Diffuse, asymptomatic, radiopaque and radiolucent intraosseous areas of cemento-osseous tissue that involve one or both arches.

FOCAL EPITHELIAL HYPERPLASIA: Multiple papillary or sessile areas of epithelial hyperplasia of the oral mucosa in young patients of specific population isolates that frequently regress spontaneously; the epithelium is extensively thickened and contains koilocytes and human papilloma viruses 13 and 32 (HPV-13 and HPV-32).

FOCAL FIBROUS HYPERPLASIA: Hyperplasia of fibrous connective tissue that evolves in response to chronic irritation in which there is extensive elaboration of collagen resembling scar tissue.

FUSION: A developmental dental anomaly characterized by an abnormally shaped tooth that may exhibit an unusually wide crown, a normal crown with an additional root, or other combinations that result from the union of two adjacent tooth germs united by a common dentin.

GEMINATION: A developmental dental anomaly characterized by a single-rooted tooth with either an unusually wide, partly divided crown or two separate crowns; thought to represent the result of an incompletely divided tooth germ.

GINGIVAL CYST OF THE ADULT: A small developmental odontogenic cyst of the gingival soft tissue derived from the rests of the dental lamina, exhibiting a lining of squamous to cuboidal epithelium with occasional distinctive focal thickenings similar to those seen in the lateral periodontal cyst.

GLANDULAR ODONTOGENIC CYST: A unilocular or multilocular odontogenic cyst derived from the rests of dental lamina and characterized by a lining with variable numbers of small intraepithelial glandular structures lined by cuboidal or columnar cells, often including mucus cells.

GRANULAR CELL TUMOR: A submucosal mass consisting of diffuse sheets of large cells of either nerve or muscle origin with a cytoplasm of densely packed eosinophilic granules (lysosomal bodies); it is commonly found on the dorsal surface of the tongue.

HAIRY LEUKOPLAKIA: White patches of the lateral borders of the tongue with a tendency for vertical linear folds found in latency stages of human immunodeficiency virus (HIV)-infected patients; the thickened epithelium containing an upper zone of clear cells (koilocytes), most of which contain Epstein-Barr virus.

HAIRY TONGUE: Abnormally elongated filiform papilla of the dorsal tongue that often become discolored from chromogenic bacteria or extrinsic substances.

HAND, FOOT, AND MOUTH DISEASE: A highly contagious systemic infection of coxsackievirus A subtypes (usually 9 and 16) of limited duration in which vesicular eruptions occur on the palms of hands, soles of feet, and mucosa of the anterior part of the mouth.

HEMANGIOMA: A proliferation of large (cavernous) or small (capillary) vascular channels occurring commonly in children; individual lesions have variable clinical courses.

HEMOPHILIA: A group of bleeding diseases that evolve as a consequence of hereditary or acquired defects in the production of proteins necessary for normal blood coagulation.

HEREDITARY GINGIVAL FIBROMATOSIS: A hereditary form of generalized gingival hyperplasia in which the autosomal dominant form may be associated with hypertrichosis, craniofacial deformities, epilepsy, and mental retardation.

HEREDITARY HEMORRHAGIC TELANGIECTASIA: An inherited disease in which vascular walls are defective and multiple vascular dilatations occur in the mucous membranes of the upper aerodigestive tract.

HERPANGINA: A nontreatable, mild infection caused by a mixture of coxsackie A viruses localized to the posterior soft palate and nasopharynx that consist of multiple small shallow ulcers resembling a herpetic infection that lasts for approximately 1 week.

HERPES ZOSTER: A regional occurrence of the varicella-zoster virus that appears as vesicular eruptions of the skin or mucosa in a distinctive unilateral pattern; pain persists for prolonged periods after lesions heal.

HERPETIC WHITLOW: A primary or secondary herpes simplex infection localized to the hands or fingers and acquired by direct contact with an active lesion.

HERPETIFORM ULCERS: Rare, multiple, small, diffuse, painful, superficial ulcers with episodes of long duration that occur on both gland-bearing and keratinized mucosal surfaces.

HISTOPLASMOSIS: A chronic lung infection common in the Mississippi Valley as the result of inhalation of spores of *Histoplasma capsulatum*; it may have associated intraoral lesions consisting of a chronic ulcer clinically resembling a malignancy and is best treated with amphotericin B.

HODGKIN LYMPHOMA: A malignant tumor of lymphocytes characterized by the appearance of Reed-Sternberg cells.

HYPERKERATOSIS: Excessively thickened layer of the stratum corneum composed of orthokeratin (hyperorthokeratosis) or parakeratin (hyperparakeratosis).

HYPERPARATHYROIDISM: Loss of bone mineralization (osteoporosis) because of increased parathyroid hormone secretion (primary) or increased demand for serum calcium (secondary), resulting in multiple systemic complications, loss of alveolar bone architecture, and occasionally giant cell tumor ("brown tumor").

HYPERPLASTIC GINGIVITIS: A focal or generalized fibrous hyperplasia of the marginal gingiva with an associated inflammatory response.

IMPACTED TEETH: Teeth with eruption that is impeded by a physical barrier.

IMPETIGO: Acute pustular eruptions of the perioral skin of children usually with inadequate perioral hygiene in which *Streptococcus pyogenes* and *Staphylococcus aureus* are the most common pathogens.

INFECTIOUS MONONUCLEOSIS: A debilitating infection of B lymphocytes caused by the Epstein-Barr virus that produces a marked mononuclear leukocytosis and is characterized by fatigue, malaise, lymphadenopathy, fever, and other symptoms that persist for prolonged periods; it occurs primarily in young adults.

INFLAMMATORY FIBROUS HYPERPLASIA: A proliferation of fibrous connective tissue with an associated chronic inflammation in response to chronic injury.

INFLAMMATORY PAPILLARY HYPERPLASIA: Multiple small nodules that consist of a proliferation of fibrous connective tissue with an associated chronic inflammation found under ill-fitting dentures.

INTERNAL RESORPTION: A form of tooth loss that begins within the pulpal chambers of intact teeth destroying dentin as it extends outward in a uniform pattern toward the tooth surfaces.

IRON DEFICIENCY ANEMIA: A lack of red blood cells and hemoglobin because of inadequate dietary intake of iron.

KAPOSI SARCOMA: A unique form of angiosarcoma that occurs in older patients and in those testing positive with human immunodeficiency virus (HIV). Lesions are macular or nodular, occur singularly or in multiples, and have a predilection for the palate and skin.

KERATOACANTHOMA: A benign endophytic epithelial growth appearing as a well-circumscribed keratin-filled crater on sun-exposed skin; often mistaken for squamous cell carcinoma.

LANGERHANS CELL HISTIOCYTOSIS: A probable neoplastic proliferation of Langerhans type of histiocytic cells with a wide spectrum of biologic behavior ranging from a single lesion of the mandible to diffusely distributed bone lesions in combination with organ and other soft tissue lesions; it consists of S-100 and CD1a positive histiocytes containing Birbeck granules and accompanying accumulations of eosinophils.

LATENCY: A prolonged stage of some viral infections in which the viral core is integrated within cellular components, but its presence is not detectable clinically or with the use of laboratory methods.

LATERAL PERIODONTAL CYST: A slow-growing, nonexpansile, developmental odontogenic cyst derived from one or more rests of the dental lamina, exhibiting a lining of one to three cuboidal cells and distinctive focal thickenings (plaques).

LEIOMYOMA: A benign neoplasm of smooth muscle within the oral cavity, usually of the blood vessels, that appears as a firm, movable, submucosal nodule.

LENTIGO MALIGNA MELANOMA: Slowly evolving melanoma that develops within a preexisting pigmented macular lesion on the sun-exposed skin of older patients.

LEUKEMIA: Circulating malignant leukocytes of bone marrow or lymph node origin.

LEUKOEDEMA: Accumulation of fluid within the epithelial cells of the buccal mucosa.

LEUKOPLAKIA: A clinical term used to denote mucosal conditions that produce a whiter than normal coloration of the mucous membranes.

LICHEN PLANUS: A skin disease common within the oral cavity, where it appears as either white reticular, plaque, or

erosive lesions with a prominent T-lymphocyte response in the immediate underlying connective tissue.

LICHENOID REACTIONS: The presence of lesions resembling erosive lichen planus mainly on the buccal mucosa; it is associated with the ingestion of some categories of medications and presence of other exogenous materials in the oral cavity.

LINGUAL MANDIBULAR SALIVARY GLAND DEPRESSION: A developmental concavity of the lingual cortex of the mandible, usually in the third molar area, that forms around an accessory lateral lobe of the submandibular gland and has the radiographic appearance of a well-circumscribed cystic lesion within the bone, usually below the inferior alveolar canal.

LINGUAL THYROID NODULE: A submucosal nodule of accessory thyroid tissue located in the midposterior tongue.

LIPOMA: A benign neoplasm of normal fat cells that appears as a soft, movable swelling, often with a slight yellowish coloration.

LIPOSARCOMA: A rare, malignant neoplasm of the oral cavity composed of a wide spectrum of histologic patterns of the fat cells.

LUDWIG ANGINA: Cellulitis involving fascial spaces between muscles and other structures of the posterior floor of the mouth that can compromise the airway.

LUPUS ERYTHEMATOSUS: A chronic inflammatory condition of the skin, connective tissue, and specific internal organs that has associated circulating autoantibodies to DNA and other nuclear and RNA proteins; circular whitish buccal mucosal lesions and erythematous rashes of the sun-exposed skin are common.

LYMPHANGIOMA: A benign proliferation of lymphatic vessels that occurs as a focal superficial lesion within the oral cavity and as a massive diffuse lesion of the neck (cystic hygroma).

LYMPHOEPITHELIAL CYST: A cyst with a lumen lined by a keratinizing stratified squamous epithelium and a capsule containing multiple normal lymphoid follicles and a dense accumulation of normal lymphocytes.

LYMPHOEPITHELIAL SIALADENITIS: A progressive, autoimmune, chronic inflammatory process primarily of the parotid glands in which dense infiltrates of T lymphocytes replace the acini and the residual ductal elements are stimulated to undergo hyperplasia, forming irregularly shaped islands of squamous epithelium (epimyoeplithelial islands).

MACRODONTIA: One or more teeth that are larger than normal.

MALIGNANT AMELOBLASTOMA: A lesion with the histopathologic features of common ameloblastoma in which documented metastasis has occurred.

MALIGNANT FIBROUS HISTIOCYTOMA: A malignant neoplasm of fibroblasts with a propensity to differentiate into histiocytic and fibrohistiocytic cells.

MALIGNANT SOLITARY FIBROUS TUMOR: A malignant neoplasm of fibroblasts that demonstrate a patternless histopathologic picture and label with the CD 34 marker.

MALT LYMPHOMA (MALTOMA): A variant of lymphoma that arises from mucosa associated lymphoid tissue that can be found throughout the digestive tract.

MEASLES: A highly contagious systemic viral infection contracted through the respiratory system and spread through the circulatory system with a predilection for skin blood vessels that produce a skin rash and sometimes pneumonia and encephalitis.

MEDIAN RHOMBOID GLOSSITIS: An asymptomatic, elongated, erythematous patch of atrophic mucosa of the mid-dorsal surface of the tongue caused by a chronic *Candida albicans* infection.

MELANOMA: Malignant neoplasm of melanocytes occurring on skin and mucosal surfaces; commonly has a radial and superficial initial growth period before it extends into the deeper underlying tissues and metastasizes.

MELANOTIC MACULE: Physiologic or reactive small, flat, brown areas of the mucosal surfaces caused by an increase in the production of melanin granules but not in the number of melanocytes.

MICRODONTIA: One or more teeth that are smaller than normal.

MONOMORPHIC ADENOMA: A group of benign salivary gland tumors composed of a proliferation of a single epithelial cell type that has a distinctive architectural pattern and is surrounded by a well-defined fibrous capsule. The two most common types are (1) basal cell adenoma and (2) canalicular adenoma.

MUCOCELE: Tissue swelling composed of pooled mucus that escaped into the connective tissue from a severed excretory duct.

MUCOEPIDERMOID CARCINOMA: A malignant salivary gland tumor of varying degrees of aggressiveness, composed of mucus-secreting and stratified squamous (epidermoid) epithelial cells and lacking a capsule.

MUCOUS MEMBRANE PEMPHIGOID: A desquamating condition of mucous membranes in which the autoimmune reaction occurs at the level of the basement membrane and commonly affects the gingiva before extending to other mucosal locations.

MUCUS RETENTION CYST: Swelling caused by an obstruction of a salivary gland excretory duct resulting in an epithelial-lined cavity containing mucus.

MULTIPLE ENDOCRINE NEOPLASIA SYNDROME: An autosomal dominant condition involving the parathyroids, pancreas, thyroid, and adrenals with one variant (MEN-IIB) that has an oral manifestation consisting of multiple neuroomas on the mucosal surfaces and lips.

MULTIPLE MYELOMA: A disseminated neoplasm of differentiated B lymphocytes or plasma cells located within bone.

MULTIPLE NEUROFIBROMATOSIS: An autosomal dominant hereditary condition consisting of multiple neurofibromas of the skin and mucosa and associated café au lait pigmentations of the skin with the potential for producing disfigurement and malignant transformation.

MUMPS: A viral infection contracted through the respiratory system that primarily affects one or more major salivary glands with swelling and pain; occasionally affects other organs and produces fever and malaise.

MYOFIBROMATOSIS and MYOFIBROMA: A benign, diffuse, infiltrative proliferation of myofibroblasts and mature collagen occurring within the soft tissues of the head and neck in young patients.

MYOSITIS OSSIFICANS: A rare reaction to injury of a muscle consisting of fibrosis and an associated deposition of bone resulting in pain, swelling, and limitation of motion.

NASOLABIAL CYST: A developmental cyst of the soft tissue of the anterior mucobuccal fold beneath the ala of the nose, most likely derived from remnants of the inferior portion of the nasolacrimal duct.

NASOPALATINE DUCT CYST: An intraosseous developmental cyst of the midline of the anterior palate, derived from the islands of epithelium remaining after closure of the embryonic nasopalatine duct.

NASOPHARYNGEAL CARCINOMA: An aggressive form of squamous cell carcinoma located in the nasopharynx and having varying degrees of differentiation; often first discovered as a metastatic lesion in a lateral neck lymph node.

NECROTIZING SIALOMETAPLASIA: A spontaneous condition of unknown cause, usually of the palate, in which a large area of surface epithelium, underlying connective tissue, and associated minor salivary glands become necrotic while ducts undergo squamous metaplasia.

NEURILEMOMA: A well-demarcated, benign lesion consisting of a fibroblastic proliferation of the nerve sheath cell (Schwann cell) producing distinctive patterns referred to as *Antoni A* and *Antoni B* tissue.

NEUROECTODERMAL TUMOR OF INFANCY: A benign, usually pigmented neoplasm commonly of the anterior maxilla and composed of two cell types arranged in alveolar patterns and derived from embryonic neural crest tissue.

NEUROFIBROMA: A demarcated or diffuse benign proliferation of perineural fibroblasts that are oriented in either a random pattern with a myxoid background or a nodular (plexiform) pattern.

NEUROGENIC SARCOMA: A malignant neoplasm with a poor prognosis of perineural fibroblasts or Schwann cells with a propensity to rapidly extend along the associated nerve trunk.

NEVUS: A benign, exophytic, usually pigmented, congenital lesion of the skin or mucosa composed of focal collections (nests) of rounded melanocytes (nevus cells); specific lesions are classified as intradermal (mucosal), junctional, or compound; a macular form, usually of the hard palate, composed of fusiform cells, is termed *blue nevus*.

NICOTINE STOMATITIS: A diffuse white change of the palate, buccal mucosa, or both caused by a combination of hyperkeratosis and acanthosis, frequently exhibiting multiple small dimpled nodules around minor salivary duct openings; found primarily in chronic pipe smokers.

NODULAR FASCIITIS: A localized, benign lesion composed of fibroblasts and myofibroblasts that is often clinically mistaken for a malignancy.

NODULAR MELANOMA: A form of melanoma of the skin and occasionally the mucosa that arises as a raised mass with a limited macular radial-growth phase; it quickly invades and metastasizes and consists of a wide variety of cell shapes and sizes.

NON-HODGKIN LYMPHOMA: A malignant neoplasm of lymphocytes lacking Reed-Sternberg cells.

NORTH AMERICAN BLASTOMYCOSIS: An uncommon, rarely symptomatic, chronic lung infection caused by inhalation of spores of *Blastomyces dermatitidis*; associated

skin lesions and occasional chronic mouth ulcers resemble malignancy and are best treated with amphotericin B.

ODONTOGENIC CARCINOMA: An aggressive and destructive intraosseous lesion of the mandible or maxilla that consists of poorly differentiated epithelial cells and clear cells in a pattern that is reminiscent of early odontogenesis.

ODONTOGENIC CYST: A cyst in which the lining of the lumen is derived from epithelium involved in tooth development.

ODONTOGENIC FIBROMA: A peripheral or intraosseous (central) benign neoplasm derived from connective tissue of odontogenic origin containing widely scattered islands and strands of embryonic odontogenic epithelium and calcifications.

ODONTOGENIC KERATOCYST: A cyst derived from the remnants (rests) of the dental lamina, with a biologic behavior similar to a benign neoplasm, with a distinctive lining of six to ten cells in thickness, and that exhibits a basal cell layer of palisaded cells and a surface of corrugated parakeratin.

ODONTOGENIC MYXOMA: An aggressive intraosseous lesion derived from embryonic connective tissue associated with odontogenesis and primarily consisting of a mucoid ground substance with widely scattered undifferentiated spindled mesenchymal cells.

ODONTOMA: A usually hamartomatous lesion commonly found over unerupted teeth, containing enamel, dentin, pulp, and cementum in either recognizable tooth shapes (compound) or a solid gnarled mass (complex).

ONCOCYTOMA: A benign salivary gland tumor occurring primarily in the parotid gland that is composed of clusters of eosinophilic granular cells (oncocytes) containing abundant mitochondria arranged in an organoid pattern and surrounded by an intact fibrous capsule.

ORAL LYMPHOEPITHELIAL CYST: A lymphoepithelial cyst commonly located intraorally on the posterior lateral tongue and the anterior floor of the mouth.

ORAL SUBMUCOUS FIBROSIS: Diffuse firm whitish areas of submucosal scarring usually caused by frequent and prolonged contact with betel nut quids, tobacco, or hot chili peppers; lesions have a higher than normal risk of developing squamous cell carcinoma.

ORAL-CERVICOFACIAL ACTINOMYCOSIS: An acute, deep, suppurative abscess of the upper neck, perioral area, and jaws with an associated draining sinus tract that contains sulfur granules and purulent exudate caused by the filamentous anaerobic gram-positive bacteria (*Actinomyces israelii*).

OROFACIAL GRANULOMATOSIS: A clinicopathologic term describing a group of oral conditions of varying causes, all with a similar microscopic feature of noncaseating granulomas.

OSSEOUS AND CARTILAGINOUS CHORISTOMA: A raised, firm, movable soft tissue nodule containing a central nidus of bone, cartilage, or both with self-limiting growth.

OSTEOGENESIS IMPERFECTA: A spectrum of diseases of bone caused by a basic alteration in the formation of the bone and connective tissue matrix, resulting in an inability of the matrix to fully mineralize, a tendency for multiple broken bones, blue sclera of the eyes, and associated dentinogenesis imperfecta.

OSTEOGENIC SARCOMA: The most common of the malignant neoplasms derived from bone cells that, in the jaws, exhibit radiographic widening of periodontal membrane of teeth and histologically exhibit a wide spectrum of findings, all of which contain atypical osteoblasts and abnormal bone or osteoid formation.

OSTEOID OSTEOMA AND OSTEOLASTOMA: Benign intraosseous lesions with similar clinical, radiographic, and histopathologic features consisting of well-demarcated, rounded intraosseous swellings, each with an active cellular central nidus surrounded by a wide zone of osteoid, with pain upon palpation.

OSTEOMA: An exophytic nodular growth of dense cortical bone on or within the mandible or maxilla in locations other than those occupied by tori or exostoses.

OSTEOMYELITIS: An inflammatory process within medullary (trabecular) bone that involves the marrow spaces.

OSTEOPETROSIS: A generalized hereditary condition consisting of excessive bone mineralization, resulting in altered stature, frequent fractures, lack of bone marrow hematopoietic function, and a tendency for severe osteomyelitis of the jaws.

OSTEORADIONECROSIS: An acute form of osteomyelitis with sequestrum formation caused by severe radiation damage to intraosseous blood vessels predisposing to areas of refractory infection and necrosis that is most commonly found in the mandible.

PAGET DISEASE: Uncoordinated increase in the osteoclastic and osteoblastic activity of the bone cells of older adults, producing larger but weaker bones, extensive pain, high levels of serum alkaline phosphatase and urinary hydroxyproline, and an increased tendency to develop malignant bone neoplasms.

PALISADED ENCAPSULATED NEUROMA: A benign hyperplastic proliferation of neurites and nerve sheath cells that are enveloped by a well-defined perineural capsule.

PAPILLARY CYSTADENOMA LYMPHOMATOSUM: A benign salivary gland lesion with limited growth potential, primarily occurring in the tail lobe of the parotid gland; it is composed of cystic spaces with intraluminal projections lined by a double cell layer of eosinophilic columnar cells and contains abundant lymphoid tissue in the underlying connective tissue.

PARADENTAL CYST: A cyst of odontogenic origin commonly located subgingivally on the buccal aspect of an erupted mandibular molar (bifurcation cyst) or the distal surface of a partially erupted mandibular third molar.

PARTIAL ANODONTIA (HYPODONTIA): The congenital absence of one or more teeth.

PARULIS: A sessile nodule on the gingiva at the site where a draining sinus tract reaches the surface.

PEMPHIGUS VULGARIS: A desquamating condition of the oral mucosa and skin in which autoantibodies destroy antigenic components of the desmosomes of the intermediate cells, producing epithelial separation above the basal cell layer.

PERIAPICAL CEMENTAL DYSPLASIA: Asymptomatic diffuse periapical radiolucent and radiopaque areas, primarily of the anterior mandible, in which cemento-osseous tissue replaces the normal architecture of bone.

PERIAPICAL CYST: An odontogenic cyst derived from rests of Malassez that proliferate in response to inflammation.

PERIPHERAL GIANT CELL GRANULOMA: An extrasosseous nodule composed of a proliferation of mononuclear and multinucleated giant cells with an associated prominent vascularity found on the gingiva or alveolar ridge.

PERIPHERAL OSSIFYING FIBROMA: A gingival nodule consisting of a reactive hyperplasia of connective tissue containing focal areas of bone.

PERNICIOUS ANEMIA: Impaired red blood cell maturation secondary to insufficient vitamin B₁₂ as the result of a defective intrinsic factor required for its absorption through the intestinal wall.

PLEOMORPHIC ADENOMA: The most common of the benign salivary gland tumors composed basically of a proliferation of myoepithelial cells and a wide spectrum of epithelial and mesenchymal tissue components and surrounded by a distinctive fibrous capsule.

POLYMORPHOUS LOW-GRADE ADENOCARCINOMA: A malignant salivary gland tumor with a predilection for the minor glands and composed of a wide variety of lobular and cribriform patterns in the central areas and laminated single-file tubular patterns in the periphery; it has a low potential for metastasis.

PRIMARY INTRAOSSEOUS CARCINOMA: A squamous cell carcinoma within the mandible or maxilla with no indication that it originated from surface epithelium or that it metastasized from another site.

PROGRESSIVE SYSTEMIC SCLEROSIS (SCLERODERMA): A generalized condition characterized by replacement of the normal connective tissue with dense collagen bundles resulting in fibrosis, loss of mobility, and altered function of organs.

PROLIFERATIVE VERRUCOUS LEUKOPLAKIA: Diffuse white and/or papillary ("warty") areas of the oral mucosa resulting from varying degrees of epithelial hyperplasia; has the potential to develop into verrucous carcinoma or well-differentiated squamous cell carcinoma.

PSEUDOEPITHELIOMATOUS HYPERPLASIA: An excessive but benign proliferation of squamous epithelium that histologically resembles the proliferation seen in a squamous cell carcinoma.

PULPITIS: An inflammation of the pulpal tissue that may be acute or chronic, with or without symptoms, and reversible or irreversible.

PYOGENIC GRANULOMA: A fast-growing reactive proliferation of endothelial cells commonly on the gingiva and usually in response to chronic irritation.

RECURRENT HERPES LABIALIS: Episodic occurrences of a cluster of vesicles and shallow ulcers localized to the lateral aspects of the lips in patients with latent herpes simplex infections; viruses dormant in ganglia that innervate the lips are triggered by a variety of internal and external factors.

RECURRENT INTRAORAL HERPES: Episodic occurrences of an intraoral cluster of symptomatic shallow punctate ulcers, commonly but not exclusively on the mucosa overlying the greater palatine foramina and typically appearing after dental procedures in the area.

REGIONAL ODONTODYSPLASIA: A developmental disturbance of several adjacent teeth in which the enamel and

dentin are thin and irregular and fail to adequately mineralize; surrounding soft tissue is hyperplastic and contains focal accumulations of spherical calcifications and odontogenic rests.

RHABDOMYOSARCOMA: A rare, rapidly growing, malignant neoplasm of striated muscle that occurs in three histologic patterns (embryonal, alveolar, and pleomorphic); all have a poor prognosis.

RHINOCEREBRAL ZYGOMYCOSIS: A chronic destructive infection of the midface and nasal passages, occurring in patients with uncontrolled diabetes mellitus, neutropenia, and severe immunocompromised status; it is caused by members of *Mucor* or *Rhizopus* of the phylum Zygomycota and is best treated with surgical debridement, followed by amphotericin B and management of the predisposing condition.

RUBELLA: A systemic viral infection beginning in the respiratory tract and extending to the circulatory system; produces a papular skin rash, fever, and malaise that last from 1 to 2 weeks; capable of producing congenital defects during pregnancy.

SARCOIDOSIS: A chronic disease affecting the skin, mucosa, salivary glands, lungs, and other organs; it consists of multiple, noncaseating, epithelioid granulomas and fibrosis of adjacent tissue.

SCURVY: A systemic disease caused by a lack of vitamin C dietary intake in which vascular wall integrity and wound repair mechanisms are defective.

SIALADENITIS: An inflammatory response of salivary gland tissue to a wide spectrum of causative factors.

SIALOLITHIASIS: The presence of one or more oval or round calcified structures (salivary stones) in a duct of a major or minor salivary gland.

SICKLE CELL ANEMIA: An inherited defect in the structure of the hemoglobin molecule causing the erythrocyte to assume a crescent shape ("sickle") and to undergo lysis.

SINUS TRACT: A drainage pathway from a deep focus of acute infection through tissue, bone, or both to an opening on the surface.

SJÖGREN SYNDROME: A group of autoimmune conditions with a marked predilection for women, it has an intense T lymphocyte-mediated autoimmune process in the salivary and lacrimal glands as one of its most prominent components.

SMOKER'S MELANOSIS: An irregular, brownish, macular pigmentation of the oral mucosa resulting from prolonged tobacco smoking.

SOFT TISSUE OSTEOMA: A focal growth of normal-appearing bone developing within the submucosal connective tissue; it is commonly found in patients with Gardner syndrome.

SOLITARY PLASMACYTOMA: A single tumor of plasma cells often located in the soft tissue of the upper air passages.

SPINDLE CELL CARCINOMA: An uncommon form of poorly differentiated squamous cell carcinoma characterized by spindle-shaped tumor cells that resemble a fibrosarcoma.

SQUAMOUS CELL CARCINOMA: A malignant neoplasm of stratified squamous epithelium that is capable of locally destructive growth and distant metastasis.

SQUAMOUS ODONTOGENIC TUMOR: A rare, sometimes multifocal, potentially aggressive lesion derived

from odontogenic epithelium and consisting of islands of stratified squamous epithelium that commonly contain microcysts and calcifications in a dense fibrous background.

SQUAMOUS PAPILLOMA: (1) A benign exophytic papillary growth of stratified squamous epithelium. (2) A papillary focal epithelial hyperplasia common in the posterior aspect of the mouth, containing koilocytic cells and human papilloma viruses 6 and 11 (HPV-6 and HPV-11).

SUPERFICIAL SPREADING MELANOMA: Most common form of malignant melanoma, initially appearing as an irregularly shaped brown-black macular area with jagged borders and satellite lesions in which areas of nodular melanoma eventually develop.

SUPERNUMERARY TEETH: Teeth in excess of the normal number.

SURGICAL CILIATED CYST OF MAXILLA: An intrabony cyst located near the floor of the maxillary sinus lined by pseudostratified ciliated columnar epithelium, caused by implantation of normal mucus-secreting sinus epithelium during previous surgery.

SYPHILIS: A sexually transmitted local and systemic infection caused by *Treponema pallidum* with three progressive clinical stages—a primary chancre at the point of contact, a secondary skin rash and mucous patches, and tertiary (late) systemically disseminated lesions; all are effectively treated with penicillin.

TAURODONTISM: A molar with an elongated crown and apically placed furcation of the roots, resulting in an enlarged rectangular coronal pulpal chamber.

THALASSEMIA: An inherited defect in either the A or B chain of the hemoglobin molecule resulting in hemolysis.

THROMBASTHENIA: A functional group of diseases characterized by defective adherence or aggregation of platelets.

THROMBOCYTOPENIA: A decrease in the number of circulating blood platelets that can be caused by a variety of factors.

THYROGLOSSAL TRACT CYST: A cyst located above the thyroid gland and beneath the base of the tongue, with a lumen lined by a mixture of epithelial cell types derived from remnants of the embryonic thyroglossal tract and often containing thyroid tissue in the capsule.

TORUS: Rounded, smooth-surfaced, nonneoplastic growth of nodular dense bone found on the midline of the palate and lingual surfaces of the mandible.

TORUS MANDIBULARIS: An exophytic nodular growth of dense cortical bone located in the cuspid and premolar area of the lingual mandible.

TORUS PALATINUS: An exophytic nodular growth of dense cortical bone located on the midline of the hard palate.

TOTAL ANODONTIA: The congenital absence of all teeth.

TRAUMATIC ATROPHIC GLOSSITIS: Focal, sensitive, erythematous areas of the tongue that are the result of a habit in which the filiform papillae are lost, the fungiform papillae are enlarged and reddened, and the epithelium is thinned.

TRAUMATIC BONE CYST: Asymptomatic, intraosseous empty cavity of young patients located primarily within the mandible and lined by a thin loose connective tissue membrane; it is adequately treated when blood enters the space during an intraosseous biopsy.

TRAUMATIC NEUROMA: A painful nodular proliferation of nerve and fibrous tissue of the nerve sheath resulting from the futile attempt of nerve fibers to reunite with their severed distal portion.

TUBERCULOSIS: A chronic granulomatous infection of the lungs caused by *Mycobacterium tuberculosis*, which is spread by aerosols; it can occasionally have associated chronic oral ulcers, enlarged nasopharyngeal and cervical lymph nodes, or both.

VARICELLA: The primary infection of the varicella-zoster virus (VZV) acquired during childhood that produces a generalized symptomatic maculopapular rash of the skin, malaise, fever, and minor lesions throughout the oral cavity.

VERRUCA VULGARIS: A papillary focal epithelial hyperplasia commonly containing koilocytic cells of human papilloma virus 2 or 6 (HPV 2 or HPV 6); usually occurs on the hands and in the anterior aspect of the mouths of children.

VERRUCOUS CARCINOMA: A diffuse, largely exophytic, superficial spreading, highly keratinized, warty form of well-differentiated squamous cell carcinoma that is unlikely to metastasize.

VIRUS-ASSOCIATED LEUKOCYTOSIS: A marked elevation in circulating lymphocytes and monocytes in response to a viral infection.

WHITE SPONGE NEVUS: An autosomal dominant hereditary condition in which the oral mucosa is white, thickened, and folded.

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